Altogether to Beat Cushing's Syndrome

ABC

Viaggio alla (ri)scoperta della Sindrome di Cushing

Terza Edizione

Sorrento, 27-30 maggio 2014

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mercoledì 28 maggio 2014

17.00-18.00 **SESSIONE 4: IL CUSHING DOPO LA GUARIGIONE**
Moderatori: **Dario Giugliano, Andrea Isidori**

17.00-17.15 LA DEFINIZIONE DI GUARIGIONE
Monica De Leo

17.15-17.30 IL DANNO RESIDUO FISICO
Giovanni Vitale

17.30-17.45 IL DANNO RESIDUO PSICHICO ED ESTETICO
Laura Trementino

17.45-18.00 Discussione

Anna Aulinas[a,*], Elena Valassi[b], Susan M. Webb[a,b]

Endocrinol Nutr. 2014;61(1):52–61

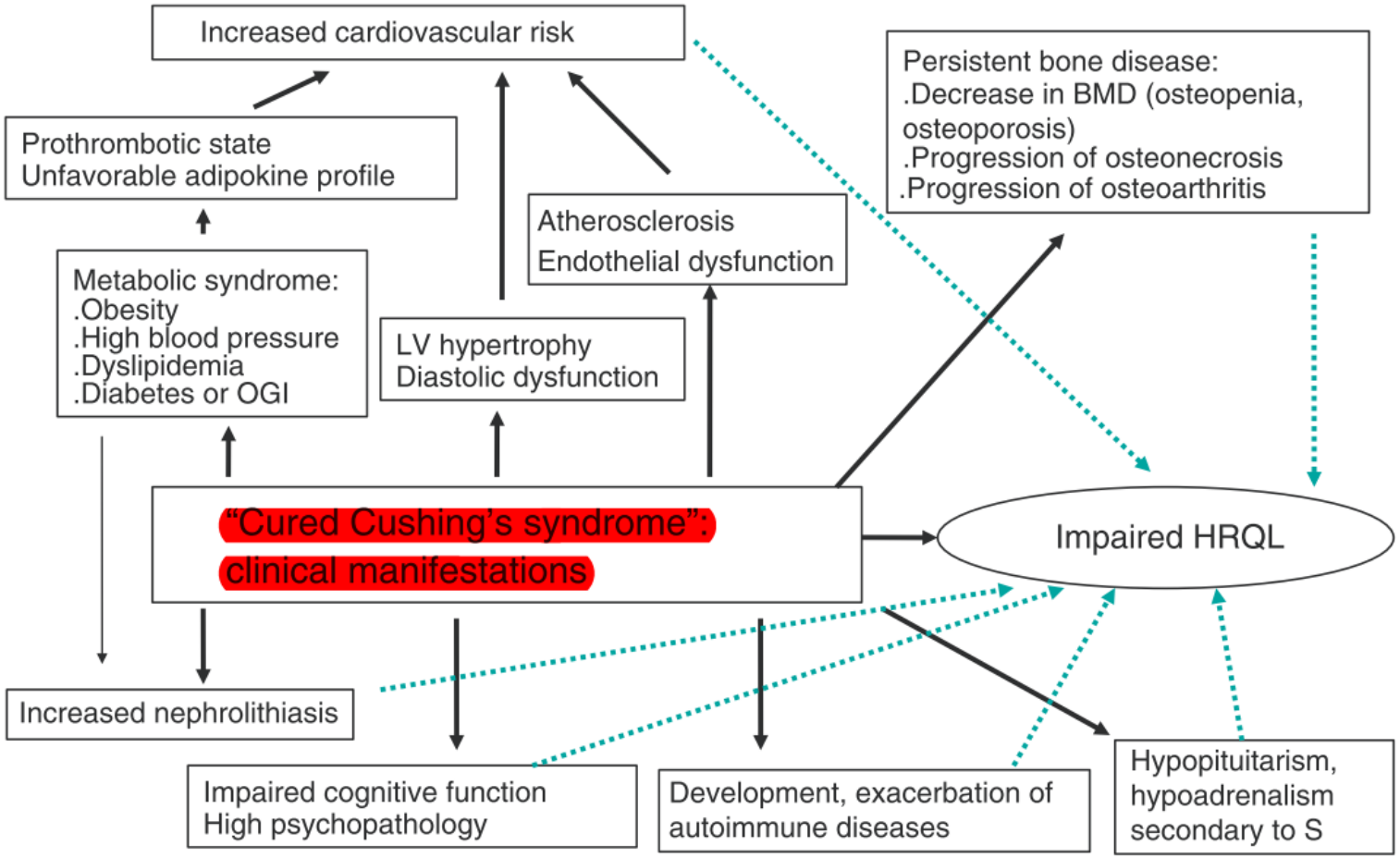

Figure 1 Schematic representation of the potential clinical manifestations and consequences despite the ''cure'' of hypercortisolism.

Endocrinol Nutr. 2014;61(1):52–61

Prognosis of patients treated for Cushing syndrome☆

Anna Aulinas[a,*], Elena Valassi[b], Susan M. Webb[a,b]

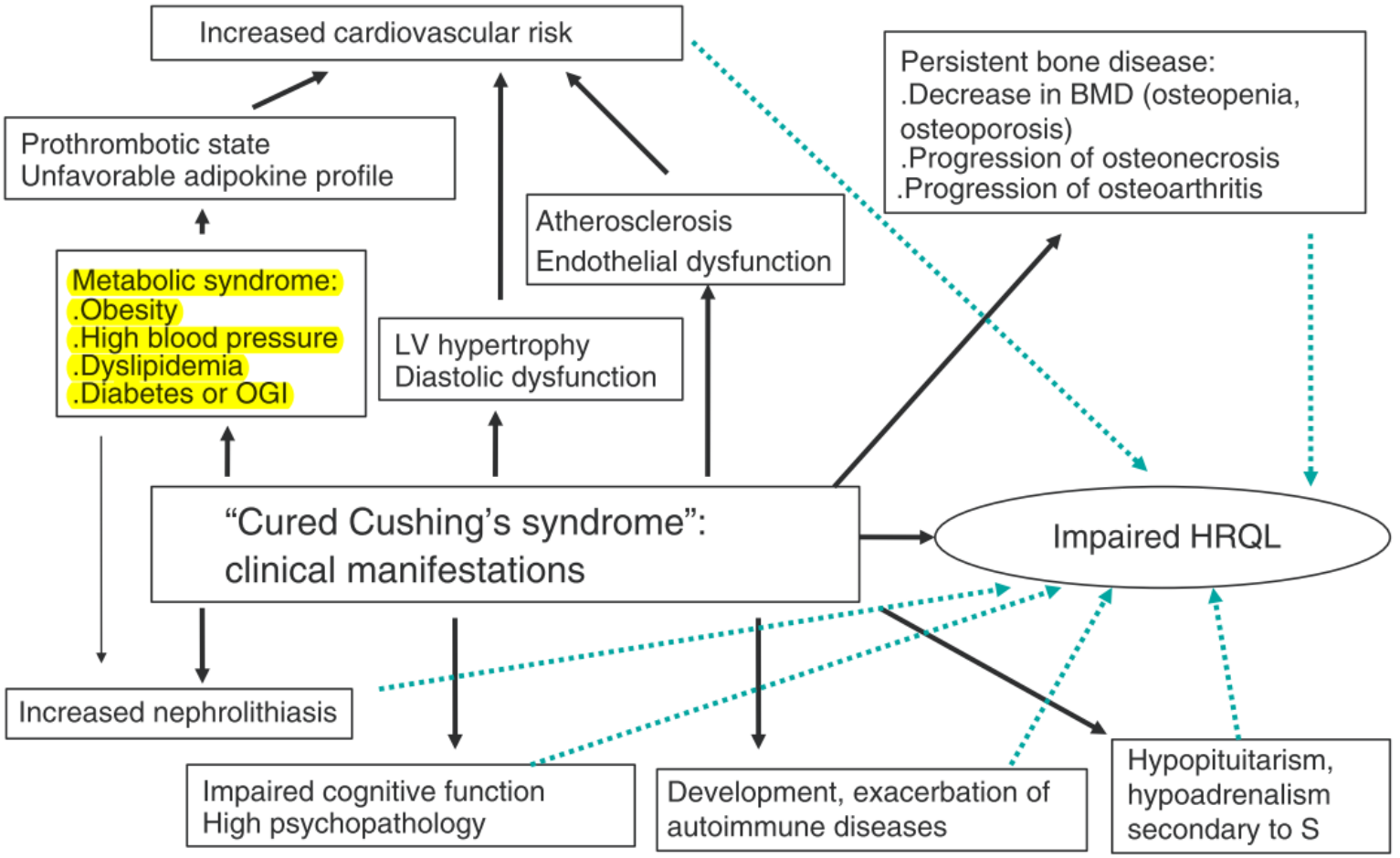

Figure 1 Schematic representation of the potential clinical manifestations and consequences despite the ''cure'' of hypercortisolism.

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

J Clin Endocrinol Metab, May 2012, 97(5):1702–1711

Fourteen CD patients were studied prospectively: before surgery (active disease) and again postoperatively 6 months after discontinuing oral glucocorticoids (remission).

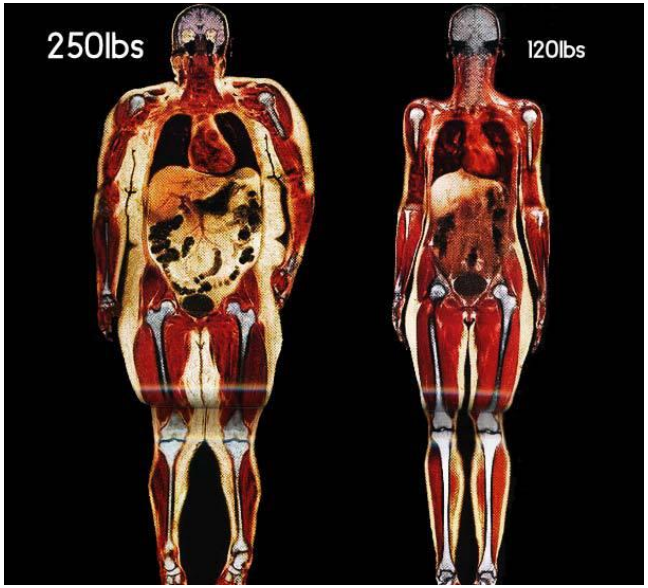

TABLE 2. Body composition measurements

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

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

J Clin Endocrinol Metab **84:** 2664–2672, 1999

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

TABLE 3. Clinical, biochemical, and hormonal features of the three groups of subjects included in the study

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

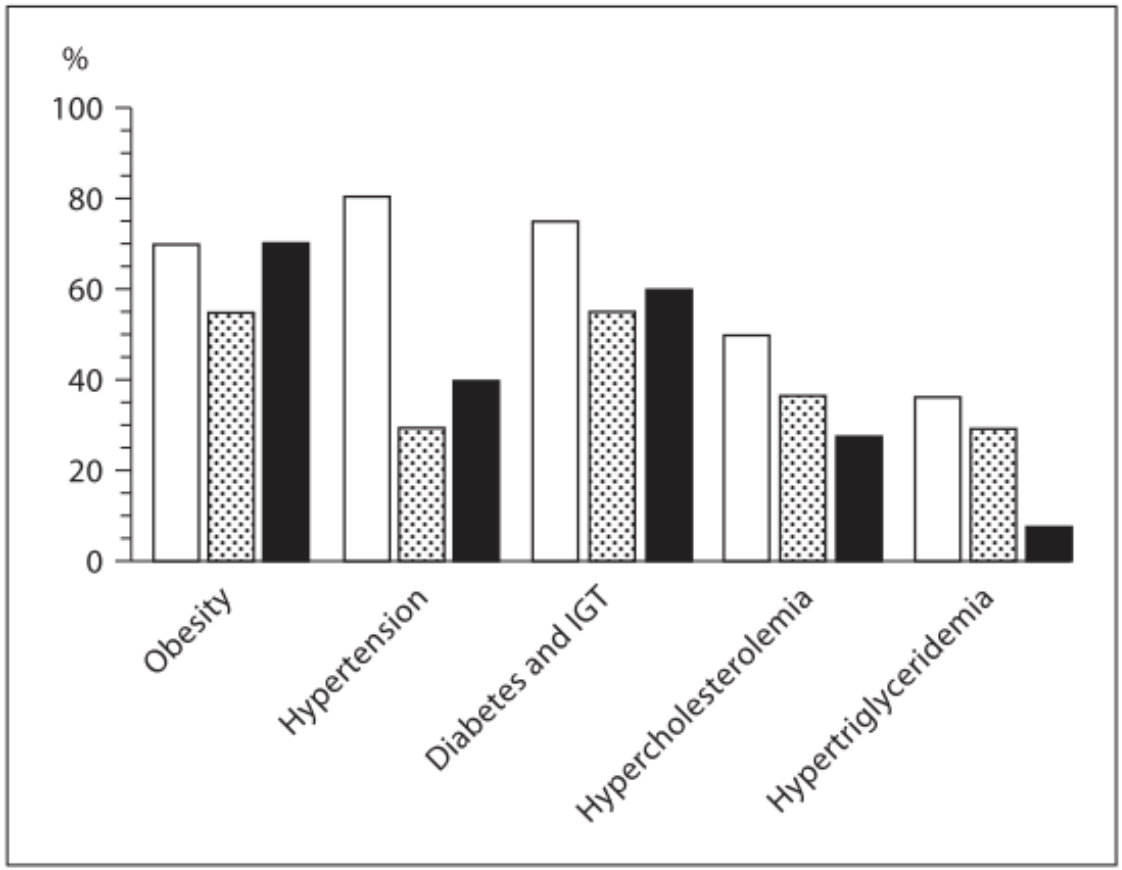

Fig. 1. Prevalence of various components of metabolic syndrome in patients with Cushing's disease before treatment □, 1 year after cure of Cushing's disease ■ and 5 years after cure of Cushing's disease ▩. IGT = Impaired glucose tolerance. Adapted from Pivonello et al. [9].

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

J Clin Endocrinol Metab, September 2009, 94(9):3365–3371

María-José Barahona, Nuria Sucunza, Eugenia Resmini, José-Manuel Fernández-Real, Wifredo Ricart, José-María Moreno-Navarrete, Teresa Puig, Jordi Farrerons, and Susan M. Webb

Patients with CS (27 of pituitary and 10 of adrenal origin) after a mean of 11 yrs of successful control of endogenous hypercortisolism.

TABLE 1. Comparison in women between cured and active CS patients and normal matched controls

	Cured CS	Active CS	Controls	*P*
n	37	14	85	
Total fat mass (%)	39.7 ± 7.4	39.4 ± 5.8	35.7 ± 6.9	<0.01[a]
Trunk fat mass (%)	40.8 ± 9	40.4 ± 7.3	34.5 ± 8.8	0.001[a]
Lean body mass (kg)	37.6 ± 6.4	39.7 ± 3.9	40.1 ± 5.3	NS
Adiponectin (ng/ml)	12.4 (5–32.4)	12.6 (8.2–26.2)	18.2 (4.5–56.5)	<0.05[a,b]
Visfatin (ng/ml)	15 (8.5–24.5)	14 (9.4–36)	13.4 (7–59)	NS
sTNF-R1 (ng/ml)	1.71 (1.07–4.28)	1.61 (1.12–2.12)	1.21 (0.79–2.47)	<0.001[a,b]
sTNF-R2 (ng/ml)	2.92 (1.65–11)	2.97 (1.05–7)	2.74 (1.62–5.59)	NS
IL-6 (pg/ml)	0.5 (0.07–11.09)	0.44 (0.17–6.74)	0.3 (0.07–1.48)	<0.001[a,b]
Insulin (pmol/liter)	54 (14–134)	66 (14–212)	35 (14–241)	<0.05[a,b]
HOMA-IR	1.61 (0.38–4.48)	2.08 (0.36–7.09)	1.09 (0.36–8.36)	NS (0.07)
Total cholesterol (mmol/liter)	5.8 ± 0.9	5.4 ± 0.7	5.4 ± 0.9	NS
HDL-c (mmol/liter)	1.6 (1.2–2.8)	1.6 (1.2–2.5)	1.7 (0.8–3.2)	NS
LDL-c (mmol/liter)	3.5 ± 0.9	3.2 ± 0.7	3.2 ± 0.8	NS
Triglycerides (mmol/liter)	1.1 (0.4–2.8)	1.0 (0.5–3.8)	0.8 (0.4–3.9)	NS
ApoB (g/liter)	1.01 ± 0.21	0.96 ± 0.16	0.89 ± 0.22	<0.05[a]
Lipoprotein a (mg/liter)	165 (70–1144)	455 (70–900)	136 (70–1177)	NS
Systolic BP (mm Hg)	130 (100–160)	135 (100–145)	120 (90–154)	<0.05[a,b]
Diastolic BP (mm Hg)	70 (60–100)	77.5 (70–100)	70 (59–94)	<0.05[b,c]
BMI (kg/m^2)	25.2 (18.7–45.5)	29.6 (23.7–34)	25.4 (19–43)	NS
Current age (yr)	50 ± 14	46 ± 12	50 ± 12	NS
Menopause (%)	43	46	50	NS

Results are expressed as mean ± SD or median (range). NS, Not significant; HOMA-IR, HOMA of insulin resistance.

[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.

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.

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.

Effects of Child- and Adolescent-Onset Endogenous Cushing Syndrome on Bone Mass, Body Composition, and Growth: A 7-Year Prospective Study Into Young Adulthood

JOURNAL OF BONE AND MINERAL RESEARCH
Volume 22, Number 1, 2007

Gary M Leong,[1,2] Veronica Abad,[1] Evangelia Charmandari,[1] James C Reynolds,[3] Suvimol Hill,[4] George P Chrousos,[1] and Lynnette K Nieman[1]

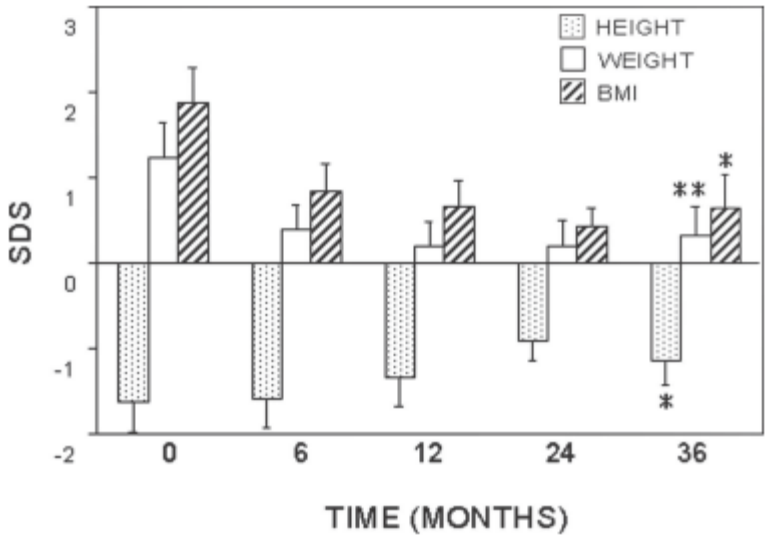

FIG. 1. Prospective changes in height, weight, and body mass index in 14 children at diagnosis and during 3 years of follow-up in remission from endogenous CS. Values are expressed as SD scores compared with age- and sex-matched normal control children.[32] Height and BMI, $*p < 0.05$; weight, $**p < 0.01$.

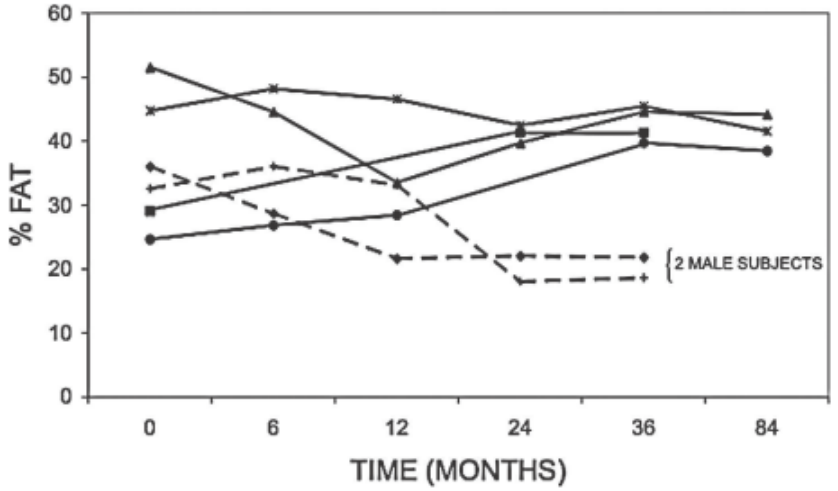

FIG. 5. Changes in total body percent fat as measured by DXA in six subjects (four females and two males in dashed lines as indicated) from diagnosis and during 3–7 years of follow-up.

Blood Pressure in Pediatric Patients with Cushing Syndrome

J Clin Endocrinol Metab. June 2009, 94(6):2002–2008

Maya B. Lodish, Ninet Sinaii, Nicholas Patronas, Dalia L. Batista, Meg Keil, Jonelle Samuel, Jason Moran, Somya Verma, Jadranka Popovic, and Constantine A. Stratakis

Data from 86 children with Cushing and 27 children with ACTH-independent CS

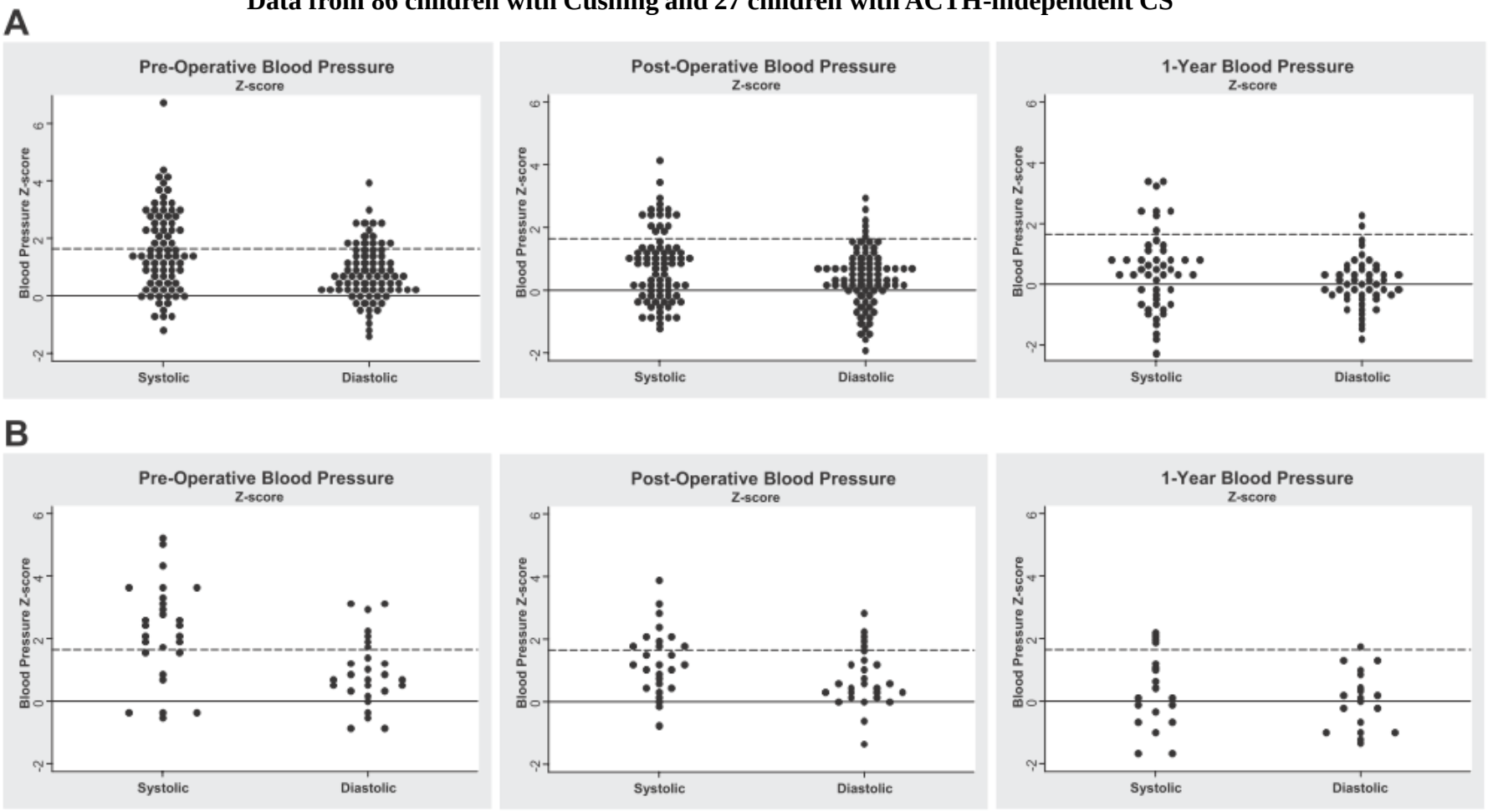

FIG. 1. Distributional scatterplots of preoperative, postoperative, and 1-yr systolic BP and diastolic BP z-scores for patients with CD (A) and AICS (B). The figures depict the extent of hypertensive subjects at each interval per patient group. *Dashed line* corresponds to the 95th percentile z-score, at or above which hypertensive status was defined.

One year postoperatively, both SHTN and DHTN were lower than the preoperative values in all patients, but as many as 16% and 4% of the patients with CD and 21% and 5% of the patients with AICS still had SHTN and DHTN, respectively.

Metabolic and cardiovascular outcomes in patients with Cushing's syndrome of different aetiologies during active disease and 1 year after remission

Clinical Endocrinology (2011) 75, 354–360

Roberta Giordano*, Andreea Picu†, Elisa Marinazzo†, Valentina D'Angelo†, Rita Berardelli†, Ioannis Karamouzis†, Daniela Forno*, Domenico Zinnà†, Mauro Maccario†, Ezio Ghigo† and Emanuela Arvat†

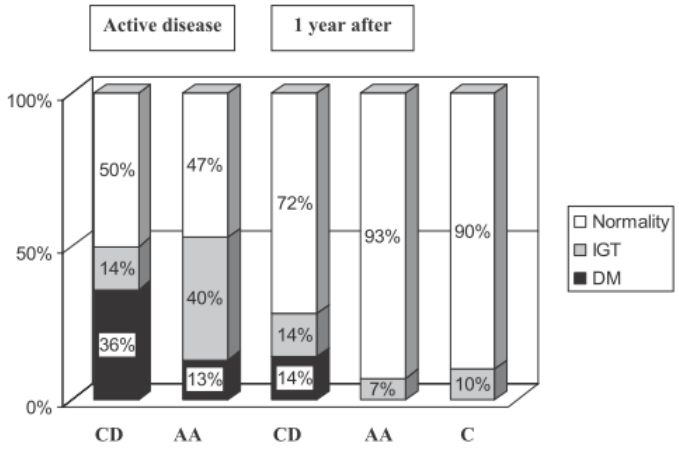

Fig. 2 Prevalence (%) of impaired glucose tolerance (IGT) and diabetes mellitus (DM) during the active disease and 1 year after hormonal remission in patients with Cushing's disease (CD), patients with Cushing's syndrome caused by adrenal adenoma (AA) and controls (C).

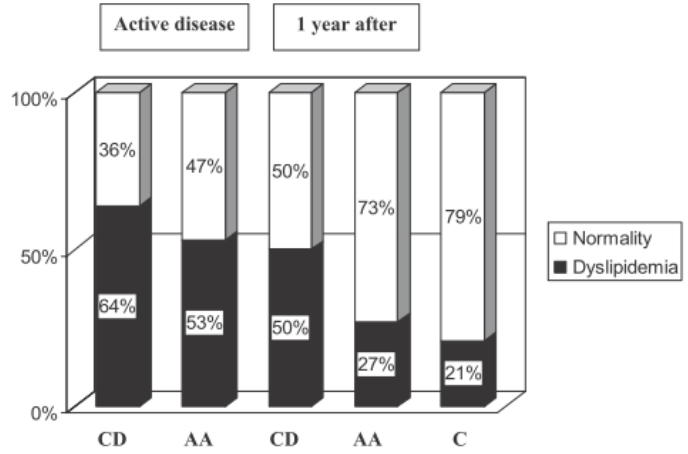

Fig. 3 Prevalence (%) of dyslipidaemia during the active disease and 1 year after hormonal remission in patients with Cushing's disease (CD), patients with Cushing's syndrome caused by adrenal adenoma (AA) and controls (C).

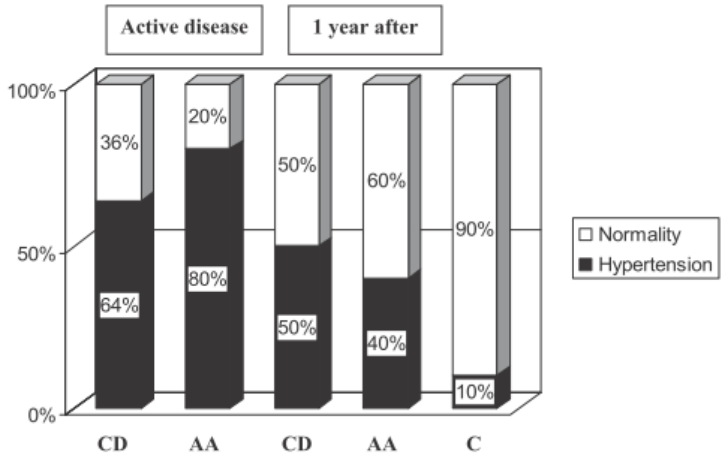

Fig. 4 Prevalence (%) of hypertension during the active disease and 1 year after hormonal remission in patients with Cushing's disease (CD), patients with Cushing's syndrome caused by adrenal adenoma (AA) and controls (C).

Patients with Cushing's syndrome are characterized by a higher prevalence of central adiposity, impaired glucose tolerance, dyslipidaemia and hypertension, if compared with age-, sex- and BMI-matched controls, regardless of its aetiology.

<u>However, 1 year after hormonal remission, patients with previous corticotrophinomas seem to maintain worse metabolic and cardiovascular outcomes than patients cured from adrenal cortisol-secreting tumours.</u>

We cannot rule out that the less favourable outcome of our patients with previous Cushing's disease may be related to multiple pituitary hormonal deficiencies and/or specific hormonal treatments.

Anna Aulinas[a,*], Elena Valassi[b], Susan M. Webb[a,b]

Endocrinol Nutr. 2014;61(1):52–61

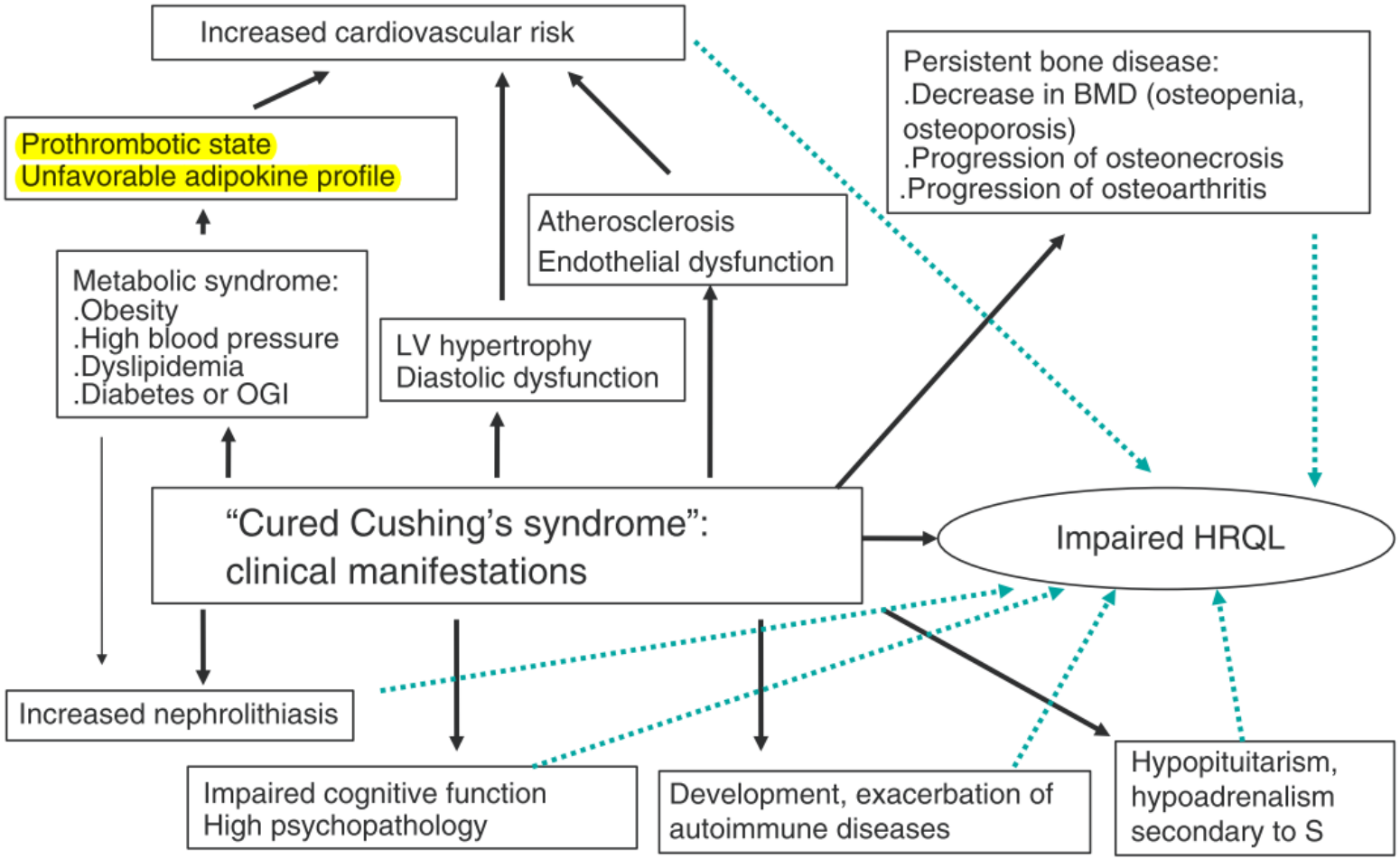

Figure 1 Schematic representation of the potential clinical manifestations and consequences despite the ''cure'' of hypercortisolism.

Adipokines and Cardiovascular Risk in Cushing's Syndrome

Neuroendocrinology 2012;95:187–206

Elena Valassi[a] Beverly M.K. Biller[a] Anne Klibanski[a] Madhusmita Misra[a, b]

Table 1. Adipokine patterns in CD

Adipokines	Pattern in active CS patients vs. BMI-matched controls	Pattern in CS after correction of hypercortisolism	
		change of levels vs. baseline	postsurgery time
Leptin	Increased [56–58, 62] Increased only in men [60] Unchanged [63]	Unchanged [58] Decreased [60, 63, 68]	10 days 9–36 months
Adiponectin	Decreased in non-obese; no difference in obese CD vs. non-obese [87] Unchanged [63, 89, 90]	Unchanged [63, 89, 90]	9–132 months
Resistin	Increased in females [63]	Unchanged [63]	9 months
TNF-α	Unchanged [68, 129, 130] Increased sTNF-R1 [90]	Increased in hypoadrenal patients [129] Increased sTNF-R1 vs. BMI-matched controls [90]	10 days 132 ± 72 months
IL-6	Unchanged [129, 130]	Increased in hypoadrenal patients [129] Increased vs. BMI-matched controls [90]	10 days 132 ± 72 months
Angiotensinogen	Increased expression of Ang II receptor 1A [166]	Not known	
PAI-1	Increased [172] Increased although not significantly [173]	Decreased vs. controls [173]	9 months
Ghrelin	Decreased [89] Increased; similar to controls with lower BMI [192]	Increased [89, 191]	3–24 months

sTNF-R1 = Soluble TNF-α receptor.

This unfavorable adipokine profiles may contribute to this state of "low grade" inflammation found in patients cured of their CS, with the resultant persistent increase in cardiovascular risk.

Coagulopathy in Cushing's Syndrome

Laura Trementino[a] Giorgio Arnaldi[a] Gloria Appolloni[a] Viviana Daidone[b]
Carla Scaroni[c] Alessandra Casonato[b] Marco Boscaro[a]

Neuro
-endocrinology
Neuroendocrinology 2010;92(suppl 1):55–59

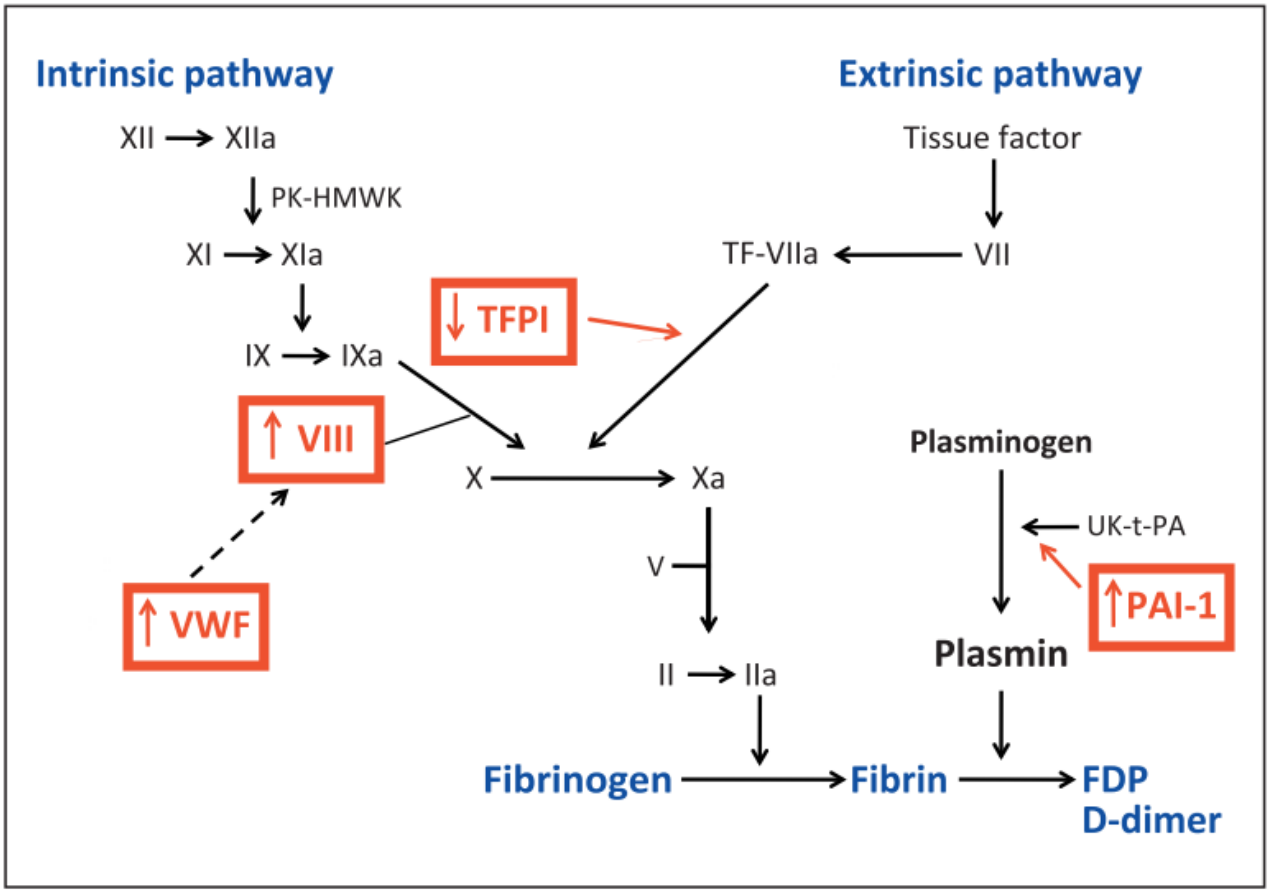

Fig. 1. Main prothrombotic alterations of clotting profile in CS. TFPI = Tissue factor pathway inhibitor.

Hyperhomocysteinemia in Patients with Cushing's Syndrome

J Clin Endocrinol Metab, August 2004, 89(8):3745–3751

MASSIMO TERZOLO, BARBARA ALLASINO, SANDRA BOSIO, ELENA BRUSA, FULVIA DAFFARA, MASSIMO VENTURA, EMILIANO AROASIO, GIANNA SACCHETTO, GIUSEPPE REIMONDO, ALBERTO ANGELI, AND CLARA CAMASCHELLA

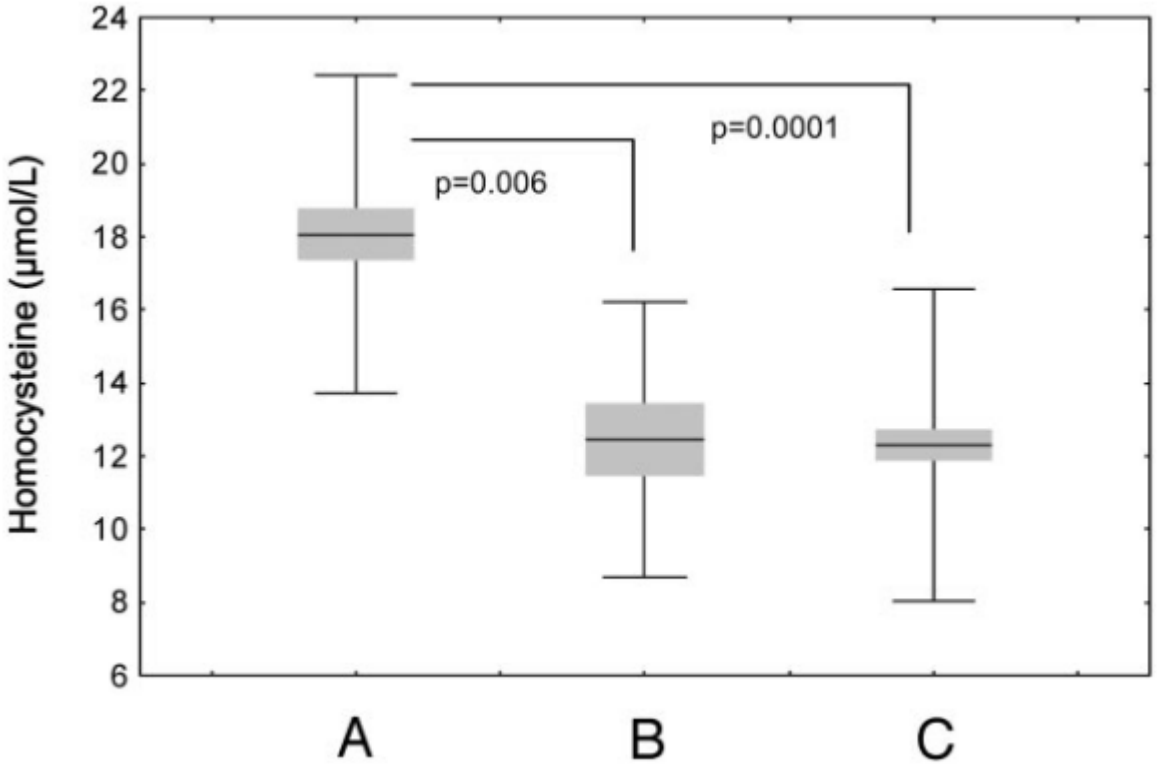

FIG. 1. Serum homocysteine concentrations in patients with active Cushing's syndrome (group A), patients in remission (group B), and healthy subjects (group C). Data are expressed as means ± SE (box) and ± SD (whisker).

Incidence of Venous Thromboembolism in Patients with Cushing's Syndrome: A Multicenter Cohort Study

J Clin Endocrinol Metab, November 2011, 96(11):3525–3532

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TABLE 2. Incidence of VTE events in CS

	Cushing patients, n	Person-years	VTE, n	Incidence rate per 1000 person-years	95% CI
Overall incidence					
VTE	473	2526	37	14.6	10.3–20.1
DVT and/or PE	473	2537	33	13.0	9.0–18.2
First-ever VTE	463	2477	34	13.7	9.5–19.1
First-ever DVT and/or PE	464	2490	30	12.0	8.1–17.2
Prior to treatment					
VTE	473	1344	19	14.1	8.5–22.0
DVT/PE	473	1345	17	12.6	7.4–20.2
First-ever VTE	463	1315	17	12.9	7.5–12.6
First-ever DVT and/or PE	464	1318	15	11.4	6.4–18.7

The risk of postoperative VTE, defined as risk within 3 months after surgery, was 0% for ACTH-independent and 3.4% (95% CI 2.0–5.9) for ACTH-dependent CS (12 events in 350 patients)

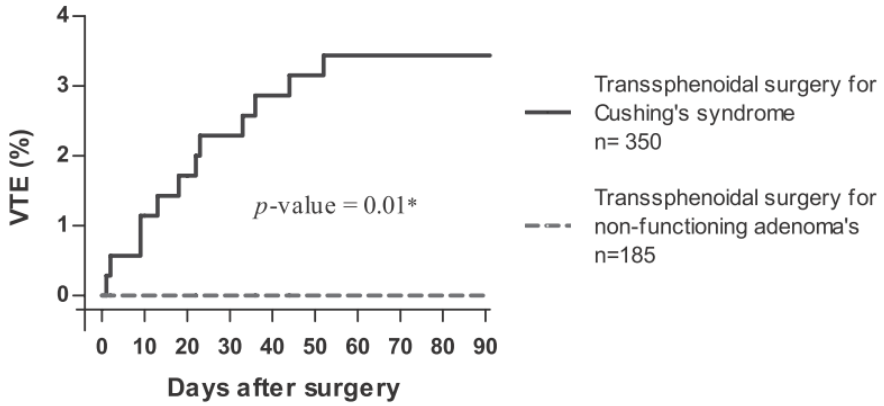


FIG. 3. Cumulative incidence of postoperative VTE. *, From log-rank test.

The Hypercoagulable State in Cushing's Disease Is Associated with Increased Levels of Procoagulant Factors and Impaired Fibrinolysis, But Is Not Reversible after Short-Term Biochemical Remission Induced by Medical Therapy

J Clin Endocrinol Metab, April 2012, 97(4):1303–1310

R. van der Pas, C. de Bruin, F. W. G. Leebeek, M. P. M. de Maat, D. C. Rijken, A. M. Pereira, J. A. Romijn, R. T. Netea-Maier, A. R. Hermus, P. M. J. Zelissen, F. H. de Jong, A. J. van der Lely, W. W. de Herder, S. W. J. Lamberts, L. J. Hofland, and R. A. Feelders

TABLE 2. Hemostatic parameters throughout the study period

	Day 0	Day 28	Day 77	*P* value	
				Days 0–28	Days 0–77
aPTT (sec)	31.5 ± 1.97	31.1 ± 1.77	30.1 ± 1.65	0.88	0.91
D-dimers (μg/ml)	0.10 ± 0.02	0.21 ± 0.08	0.13 ± 0.02	0.05	0.48
Fibrinogen (g/liter)	3.19 ± 0.20	3.05 ± 0.21	3.34 ± 0.18	0.16	0.97
Factor VIII (U/ml)	1.11 ± 0.12	1.26 ± 0.17	1.29 ± 0.13	0.47	0.22
vWF:Ag (U/ml)	1.35 ± 0.14	1.35 ± 0.15	1.49 ± 0.14	0.53	0.11
Blood group O	1.11 ± 0.30	1.03 ± 0.28	1.20 ± 0.30	0.47	0.11
Blood group non-O	1.46 ± 0.14	1.50 ± 0.15	1.54 ± 0.13	0.27	0.25
Antithrombin (U/ml)	1.04 ± 0.04	0.95 ± 0.04	0.94 ± 0.03	<0.01	<0.01
Protein C (U/ml)	1.41 ± 0.12	1.41 ± 0.12	1.33 ± 0.11	0.91	0.10
Protein S (U/ml)	1.04 ± 0.08	1.04 ± 0.09	0.99 ± 0.07	0.59	0.13
CLT (min)	134.5 ± 16.4	145.8 ± 19.2	140.6 ± 21.3	0.43	0.94
TAFI (μg/ml)	20.5 ± 0.61	19.8 ± 0.88	18.8 ± 0.78	0.19	<0.05
PAI-1 (IU/ml)	7.70 ± 3.46	10.7 ± 3.97	7.65 ± 2.46	<0.05	0.38
α2-antiplasmin (U/ml)	1.25 ± 0.04	1.21 ± 0.05	1.24 ± 0.04	0.21	0.33

Patient characteristics at baseline, d 28, and d 77 of the study period. Both patients that developed pulmonary embolism during the first month of the study were excluded from this analysis, because they were using acenocoumarol both at d 28 and 77. vWF:Ag concentrations were analyzed separately for subjects with blood group O and subjects with blood group non-O because blood group O is associated with lower levels of vWF:Ag (40). Data are expressed as mean ± SEM.

Changes in coagulation indexes and occurrence of venous thromboembolism in patients with Cushing's syndrome: results from a prospective study before and after surgery

European Journal of Endocrinology (2010) **163** 783–791

Luca Manetti, Fausto Bogazzi, Clara Giovannetti, Valentina Raffaelli, Maura Genovesi, Giovanni Pellegrini[1], Lucia Ruocco[1], Aldo Iannelli[2] and Enio Martino

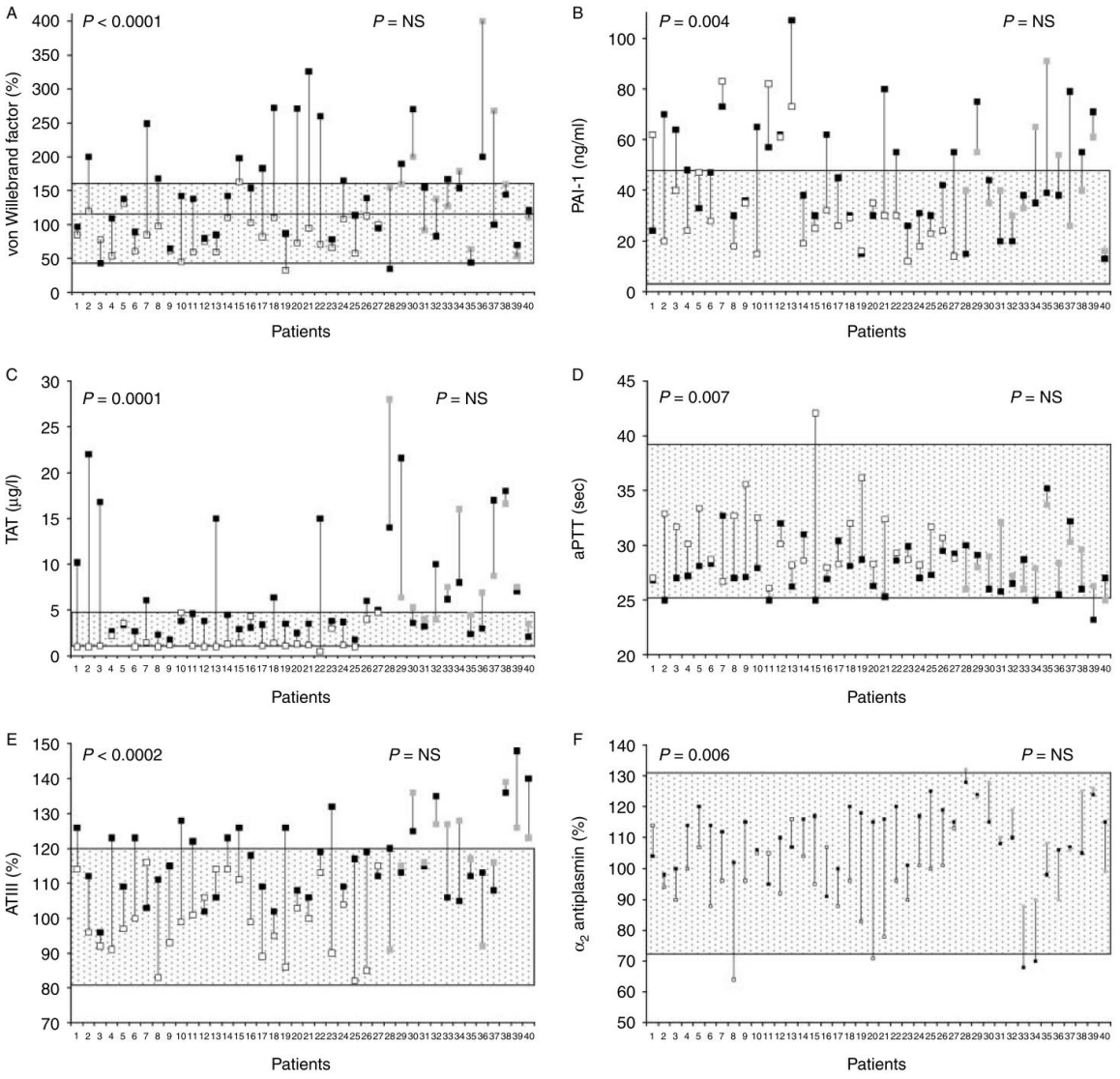


Figure 1 Changes in von Willebrand factor (A), plasminogen activator inhibitor antigen (PAI-1) (B), thrombin–antithrombin complex (TAT) (C), activated partial thromboplastin time (aPTT) (D), antithrombin III (ATIII) (E) and α_2 antiplasmin (F) in untreated patients with Cushing's syndrome before and after surgery. The black, white and grey squares indicate untreated, remission and persistence patients respectively. The grey area indicates the normal limits of each parameter. In (A), were represented two normal ranges for 0 and non-0 blood group.

Endocrinol Nutr. 2014;61(1):52–61

Prognosis of patients treated for Cushing syndrome☆

Anna Aulinas[a,*], Elena Valassi[b], Susan M. Webb[a,b]

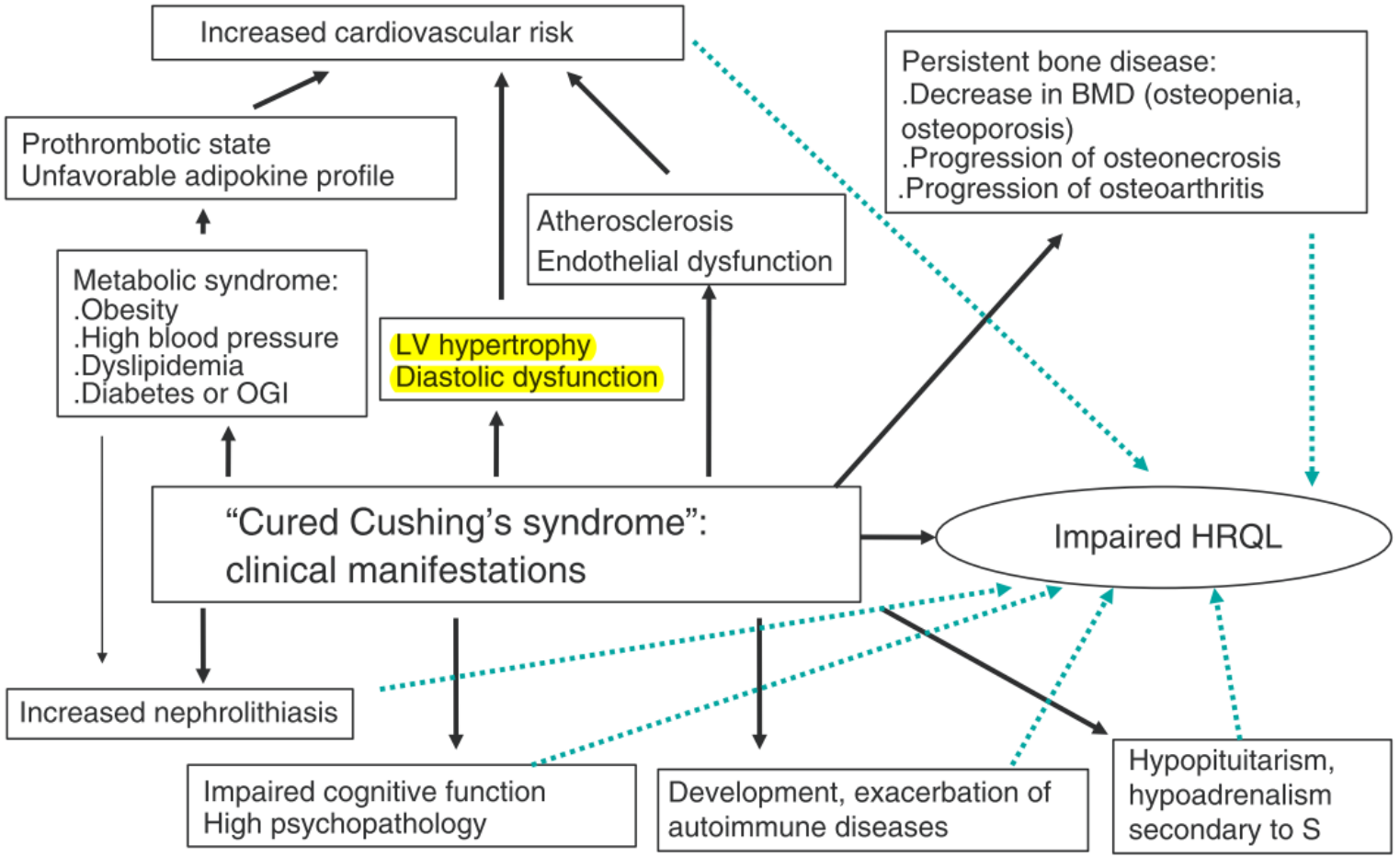


Figure 1 Schematic representation of the potential clinical manifestations and consequences despite the ''cure'' of hypercortisolism.

Clinical relevance of cardiac structure and function abnormalities in patients with Cushing's syndrome before and after cure

Clinical Endocrinology (2012) **76**, 332–338

Paola M. Toja*, Giovanna Branzi†, Francesca Ciambellotti†, Piero Radaelli‡, Martina De Martin*, Laura Maria Lonati†, Massimo Scacchi*,‡, Gianfranco Paratit,§, Francesco Cavagnini* and Francesca Pecori Giraldi*,‡

Table 2. Left ventricular parameters recorded in sonograms performed in patients with active Cushing's syndrome, after cure and in controls

	Active Cushing's syndrome	Cured Cushing's syndrome	Controls
Interventricular septum thickness (% abnormal)	69%* (10·2 ± 0·17 mm)*	47%† (9·7 ± 0·15 mm)*†	39% (9·4 ± 0·17 mm)
Posterior wall thickness (% abnormal)	49%* (9·7 ± 0·16 mm)*	36%* (9·1 ± 0·14 mm)*†	9% (8·5 ± 0·12 mm)
Left ventricular mass index (% abnormal)	46%* (46·9 ± 1·63 g/m$^{2·7}$)*	32% (44·2 ± 1·24 g/m$^{2·7}$)	19% (42·2 ± 1·63 g/m$^{2·7}$)
Relative wall thickness (% abnormal)	51%* (0·43 ± 0·01)*	33%*† (0·40 ± 0·01)*†	11% (0·37 ± 0·01)
Ejection fraction (% abnormal)	0·3% (64·3 ± 0·41%)*	0·2% (64·3 ± 0·42%)*	0% (67·9 ± 0·58%)
Mid-wall fractional shortening (% abnormal)	19%* (16·6 ± 0·24%)*	13% (17·0 ± 0·24%)*	5% (18·7 ± 0·35%)
Left atrial diameter (% abnormal)	8% (33·2 ± 0·64 mm)	2% (33·3 ± 0·42 mm)	2% (32·6 ± 0·54 mm)
E/A ratio (% abnormal)	9% (1·26 ± 0·06)	6% (1·24 ± 0·05)	5% (1·34 ± 0·06)
E-wave deceleration time (% abnormal)	41%* (197·9 ± 6·12 ms)*	35% (194·5 ± 4·44 ms)*	23% (165·7 ± 6·16 ms)
IVRT (% abnormal)	12% (85·0 ± 2·91 ms)	10% (81·1 ± 2·84 ms)	11% (78·9 ± 6·20 ms)

*$P < 0·05$ *vs* controls, †$P < 0·05$ *vs* active disease; measurements are given in parentheses. Percentages refer to abnormal findings at cardiac sonogram: 49 sonograms were performed in patients with active Cushing's syndrome, 59 in patients cured of Cushing's syndrome since at least 1 year and 70 in controls. IVRT, isovolumetric relaxation time.

Concentric hypertrophy and remodelling were still somewhat more prevalent than in controls (27% and 25% vs 12.5% and 8.9% in cardiac ultrasounds performed in patients cured of Cushing's syndrome and controls, respectively).

Parameters of systolic function, (ejection fraction and MWFS, were both comprised in the normal range in most cardiac ultrasounds performed in patients in remission, although mean values were still somewhat lower than in controls.

The prevalence of impaired relaxation, assessed by E-wave deceleration time, was comparable to controls (35% vs 23%) although mean measurements were still longer.

Clinical relevance of cardiac structure and function abnormalities in patients with Cushing's syndrome before and after cure

Clinical Endocrinology (2012) **76**, 332–338

Paola M. Toja*, Giovanna Branzi†, Francesca Ciambellotti†, Piero Radaelli‡, Martina De Martin*, Laura Maria Lonati†, Massimo Scacchi*,‡, Gianfranco Paratit†,§, Francesco Cavagnini* and Francesca Pecori Giraldi*,‡

Table 4. Left ventricular parameters according to blood pressure status

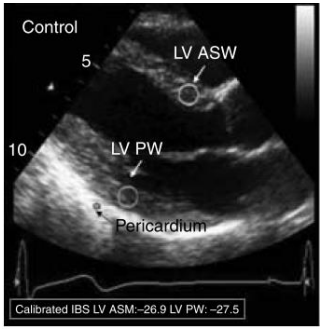
	Active Cushing's syndrome		Cured Cushing's syndrome		Controls	
	Normotension	Hypertension	Normotension	Hypertension	Normotension	Hypertension
LVMI	42·9 ± 2·34	49·3 ± 2·12*†	42·8 ± 1·36	48·7 ± 2·68†	39·3 ± 1·91	42·1 ± 1·61
IVSd	9·5 ± 0·22†	10·7 ± 0·19*†	9·6 ± 0·18†	10·1 ± 0·25†	8·8 ± 0·26	9·2 ± 0·22
PWd	9·1 ± 0·21†	10·1 ± 0·21*†	8·9 ± 0·16	9·3 ± 0·28†	8·5 ± 0·18	8·5 ± 0·16
RWT	0·41 ± 0·01†	0·44 ± 0·01*†	0·40 ± 0·01	0·41 ± 0·01†	0·36 ± 0·02	0·36 ± 0·01
EF	65·2 ± 0·65	63·7 ± 0·51†	64·7 ± 0·39	63·1 ± 0·81†	65·9 ± 0·42	67·4 ± 0·74
mwFS	17·0 ± 0·41†	16·4 ± 0·28†	17·2 ± 0·27†	16·7 ± 0·38†	18·5 ± 0·52	18·8 ± 0·47
Left atrium	30·8 ± 0·9	34·8 ± 0·74*	32·3 ± 0·47	35·3 ± 0·68*	30·0 ± 0·94	33·6 ± 0·58*
E/A	1·37 ± 0·10	1·19 ± 0·07	1·35 ± 0·06	0·99 ± 0·07*†	1·48 ± 0·06	1·27 ± 0·08*
DT E	184·7 ± 9·09	205·6 ± 7·88	192·4 ± 4·05	198·5 ± 6·35	188·4 ± 8·89	172·1 ± 7·50

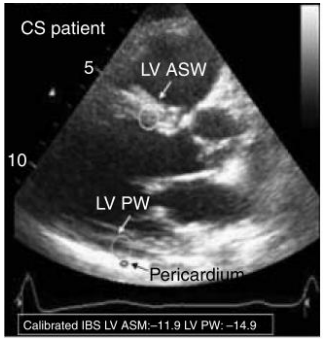
**vs* normotensive counterpart; †*vs* control counterpart. Percentages refer to abnormal findings at cardiac sonogram: 49 sonograms were performed in patients with active Cushing's syndrome, 59 in patients cured of Cushing's syndrome since at least 1 year and 70 in controls.
LVMI, left ventricular mass index; IVSd, interventricular septum thickness in diastole; PWd, posterior wall thickness in diastole; RWT, relative wall thickness; EF, ejection fraction; mwFS, mid-wall fractional shortening; E/A, early atrial peak flow velocity ratio; DT E, E-wave deceleration time.

Increased myocardial fibrosis and left ventricular dysfunction in Cushing's syndrome

European Journal of Endocrinology (2012) **166** 27–34

Kai Hang Yiu[1,2,*], Nina Ajmone Marsan[1,3,*], Victoria Delgado[1], Nienke R Biermasz[4], Eduard R Holman[1], Johannes W A Smit[4], Richard A Feelders[5], Jeroen J Bax[1] and Alberto M Pereira[4]





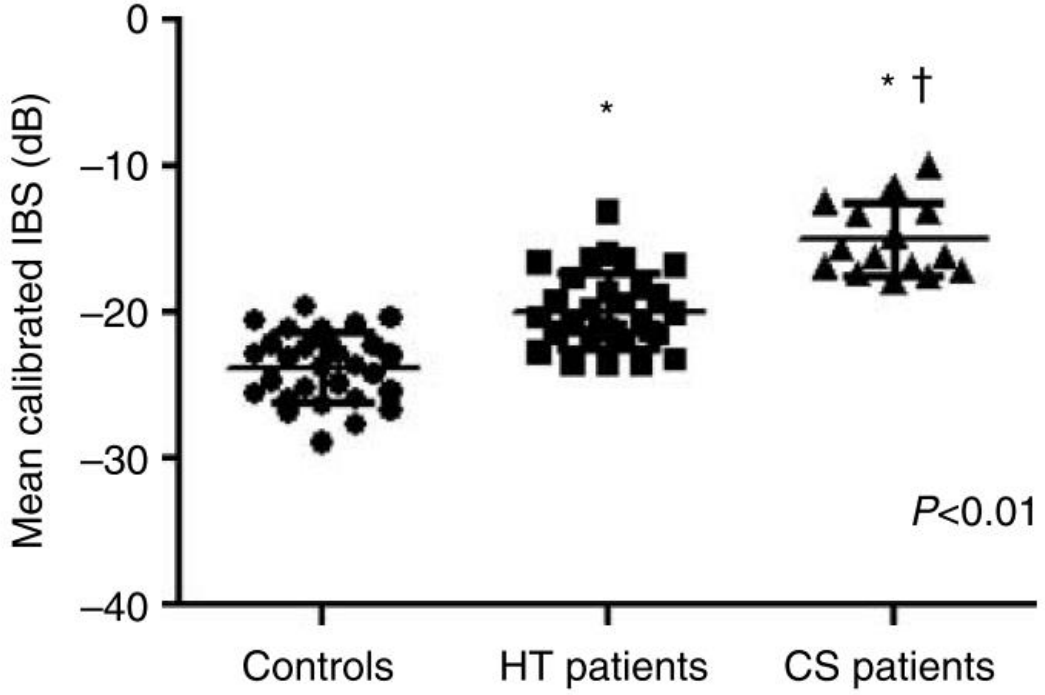


Figure 2 Comparison of mean calibrated integrated backscatter (IBS) between normal subjects (controls), hypertensive (HT) patients, and patients with Cushing's syndrome (CS) before treatment. Patients with CS show the highest mean calibrated IBS compared with HT patients and controls, suggestive of increased myocardial fibrosis. *Significant differences with controls; †Significant differences with HT patients.

Increased myocardial fibrosis and left ventricular dysfunction in Cushing's syndrome

European Journal of Endocrinology (2012) **166** 27–34

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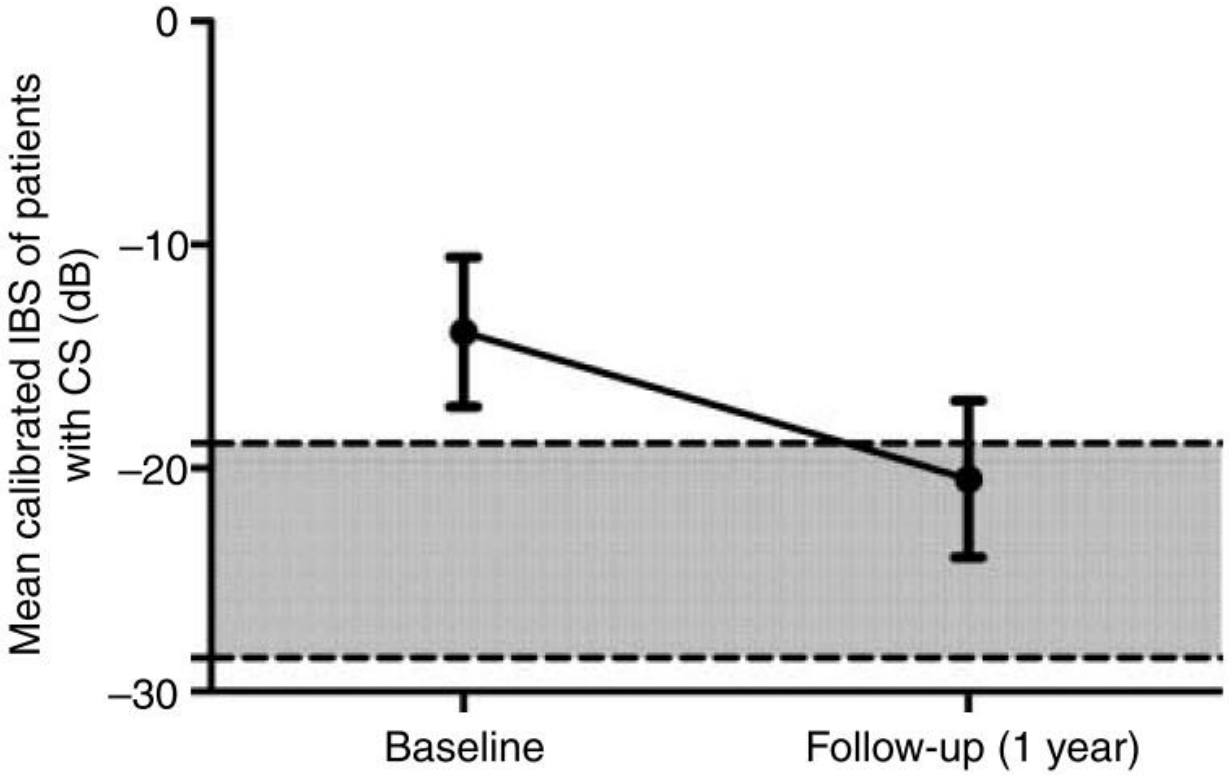

Figure 3 Mean calibrated integrated backscatter (IBS) in patients with Cushing's syndrome (CS) before (baseline) and after surgical treatment (follow-up). The shaded area represents the normal range of mean calibrated IBS, derived from the control group as the mean value ± 2 S.D. Upon successful surgical treatment, the mean calibrated IBS in CS patients significantly decreased ($P<0.01$) and reached the range of normal values, suggesting the reversibility of myocardial fibrosis.

Anna Aulinas[a,*], Elena Valassi[b], Susan M. Webb[a,b]

Endocrinol Nutr. 2014;61(1):52–61

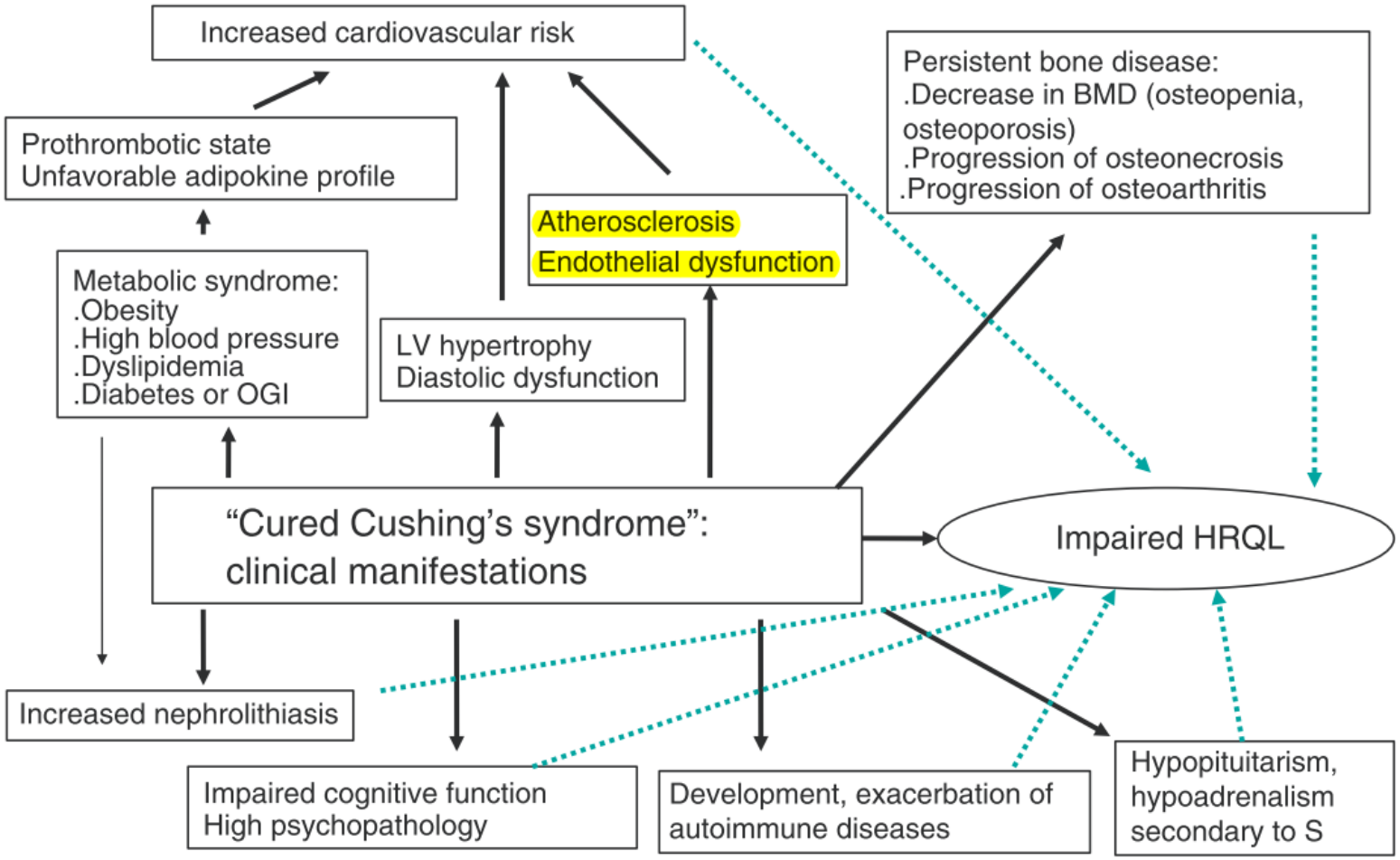

Figure 1 Schematic representation of the potential clinical manifestations and consequences despite the ''cure'' of hypercortisolism.

Endocrine Journal 2010, **57** (3), 245-252

ITARU AKAZA, TAKANOBU YOSHIMOTO, KYOICHIRO TSUCHIYA AND YUKIO HIRATA

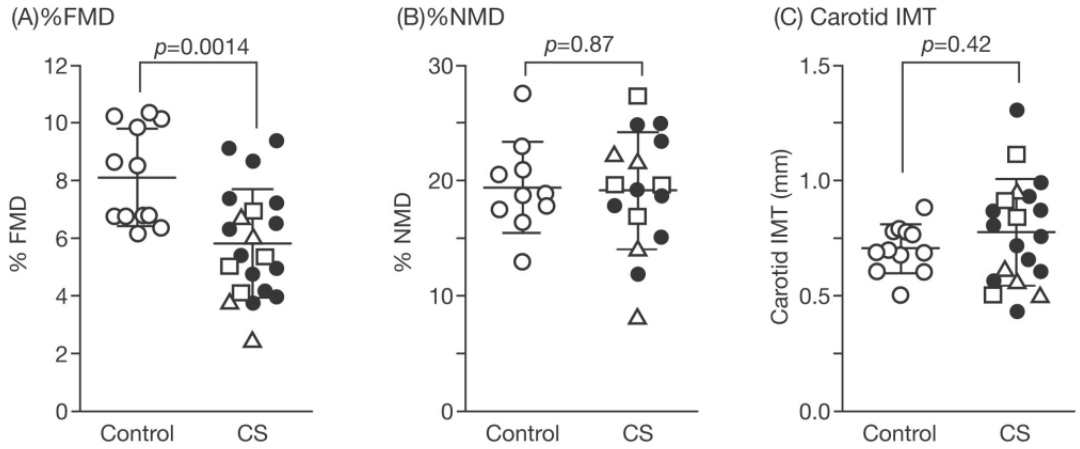

Fig. 1. Endothelium-dependent and -independent vasodilation and carotid intima-media thickness (IMT) in control subjects and patients with Cushing's syndrome (CS).
(A) %FMD, (B) %NMD and (C) carotid IMT are shown in 12 control subjects (○) and 21 CS patients: (□) Cushing's disease (4), (△) ectopic ACTH syndrome (4), (●) adrenal adenoma (13).

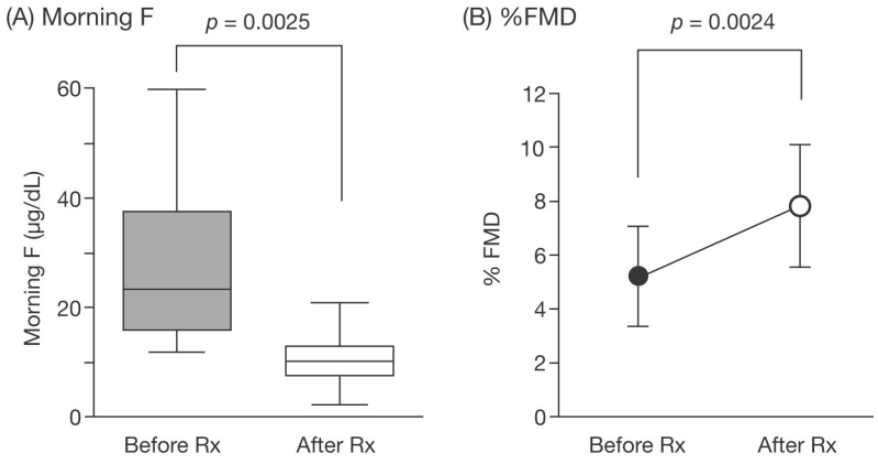

Fig. 3. Changes of morning F and %FMD in CS patients before and after treatment.
Changes of (A) morning F before (▪) and after (▫) treatment (Rx), and (B) %FMD (mean±SD) before (●) and after (○) Rx in 12 CS patients are shown.

Cardiovascular Risk Factors and Common Carotid Artery Caliber and Stiffness in Patients with Cushing's Disease during Active Disease and 1 Year after Disease Remission

J Clin Endocrinol Metab, June 2003, 88(6):2527–2533

ANTONGIULIO FAGGIANO, ROSARIO PIVONELLO, STEFANO SPIEZIA, MARIA CRISTINA DE MARTINO, MARIAGIOVANNA FILIPPELLA, CAROLINA DI SOMMA, GAETANO LOMBARDI, AND ANNAMARIA COLAO

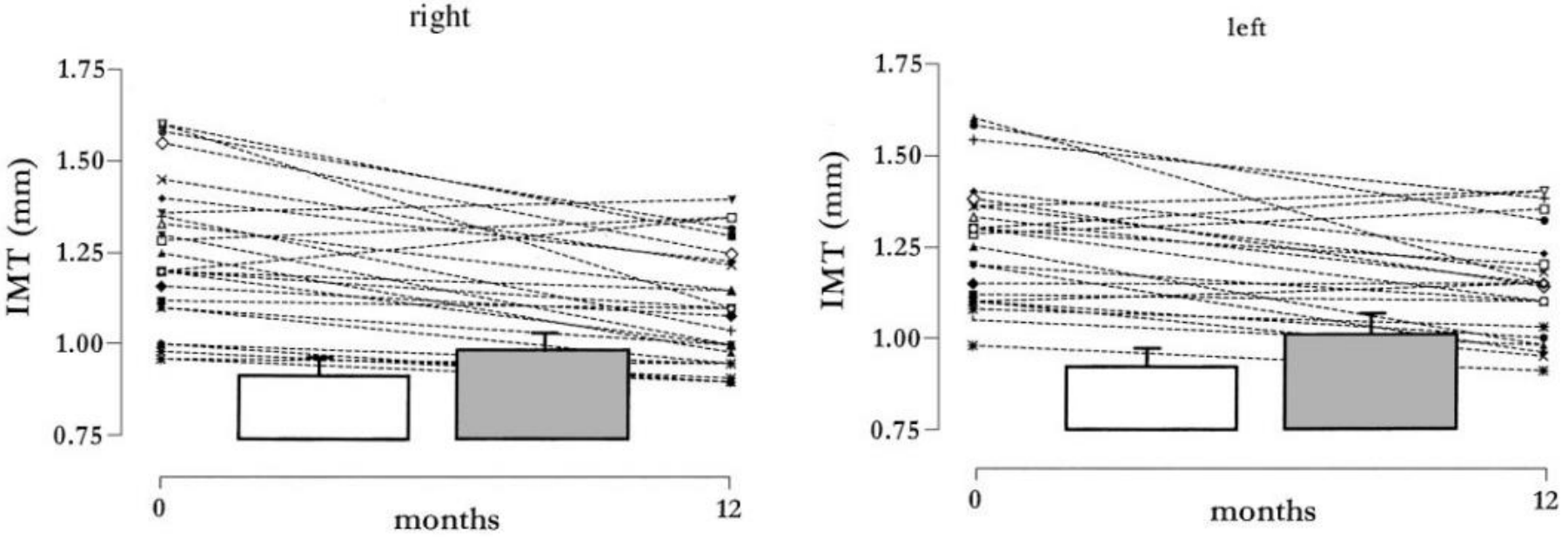

FIG. 1. Individual data of the right and left IMT before and 1 yr after remission from CD, measured by ultrasonography. The *bar* indicates the IMT of control-1 (□) and control-2 (▨) subjects expressed as mean ± SEM.

32 sex- and age-matched healthy subjects (control-1) and 32 BMI-matched subjects (control-2).

Coronary Artery Disease Detected by Multislice Computed Tomography in Patients After Long-Term Cure of Cushing's Syndrome

J Clin Endocrinol Metab, March 2013, 98(3):1093–1099

María-José Barahona, Eugenia Resmini, David Viladés, Guillem Pons-Lladó, Rubén Leta, Teresa Puig, and Susan M. Webb

Table 2. Comparison Between Cured CS Women and Their Respective Controls

	Cured CS	Controls	*P*
n	24	34	
Menopause	45.8%	44%	NS
Smokers	25%	38%	<.05
Diabetes	0	0	NS
Arterial hypertension	29%	5.8%	<.05
Body mass index, kg/m^2	26.5 (18.8–37.4)	23.4 (17.5–39)	<.05
Current age, y	50 ± 14	46 ± 12	NS
Coronary calcifications	29% (7/24)	12% (4/34)	NS
Agatston score	26 (1–269)	33 (3–76)	NS
Noncalcified plaques	17.6% (3/17)	6.6% (2/30)	NS
Significant stenosis	0	0	NS
Abnormal MDCT	42% (10/24)	18% (6/34)	<.05

Abbreviations: MDCT, multidetector computed tomography; NS, not significant. Results are expressed as mean ± SD or median and range in parentheses.

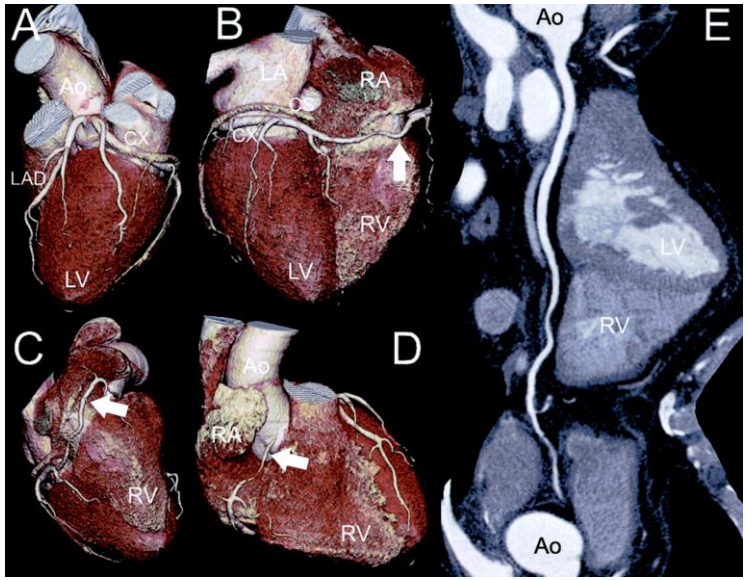

Table 3. Comparison Between Young Cured CS Patients (<45 y) and Their Respective Controls

	Cured CS	Controls	*P*
n	10	20	
Sex (male/female) (n)	1/9	4/16	
Smokers	40%	35%	NS
Diabetes	0	0	NS
Arterial hypertension	0	0	NS
Body mass index, kg/m^2	24.5 (18.8–35.6)	23 (17.8–35.5)	NS
Current age, y	36.6 ± 6	35.3 ± 5	NS
Coronary calcifications	0	0	NS
Noncalcified plaques	30% (3/10)	0	.01
Significant stenosis	0	0	NS
Abnormal MDCT	30% (3/10)	0	.01

Abbreviations: MDCT, multidetector computed tomography; NS, not significant. Results are expressed as mean ± SD or median and range in parentheses.

Anna Aulinas[a,*], Elena Valassi[b], Susan M. Webb[a,b]

Endocrinol Nutr. 2014;61(1):52–61

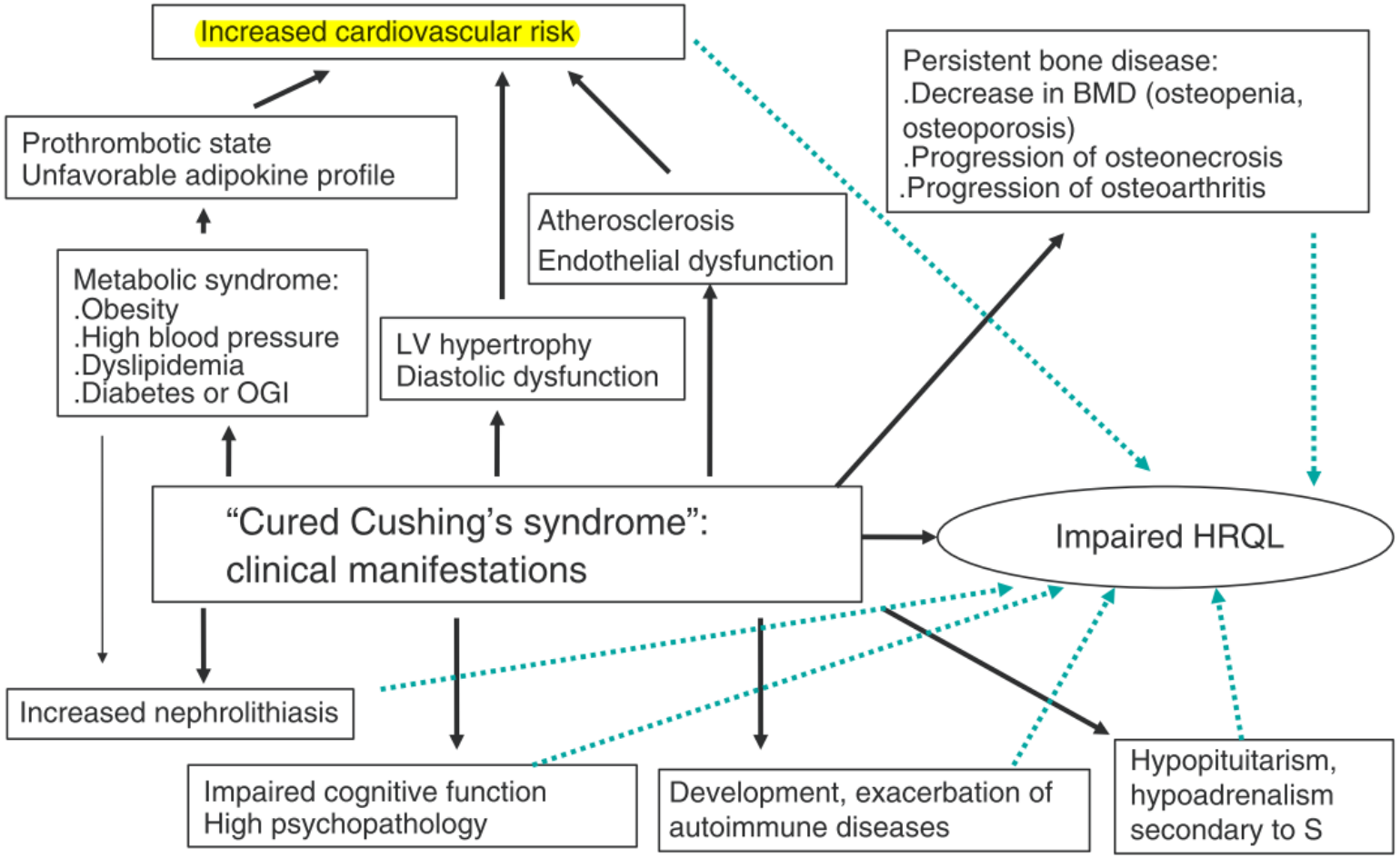

Figure 1 Schematic representation of the potential clinical manifestations and consequences despite the ''cure'' of hypercortisolism.

Anna Aulinas[a,*], Elena Valassi[b], Susan M. Webb[a,b]

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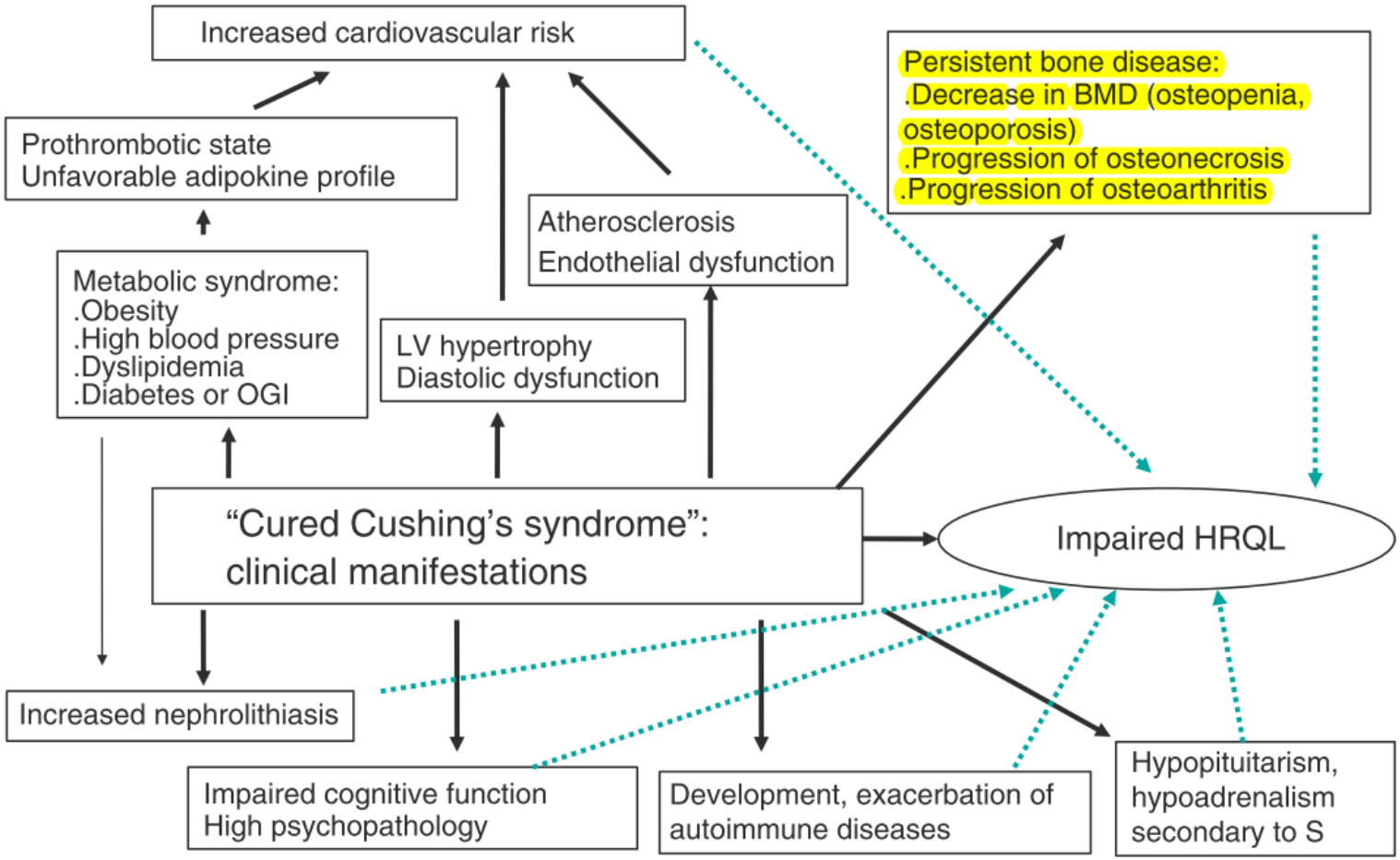

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Anna Aulinas[a,*], Elena Valassi[b], Susan M. Webb[a,b]

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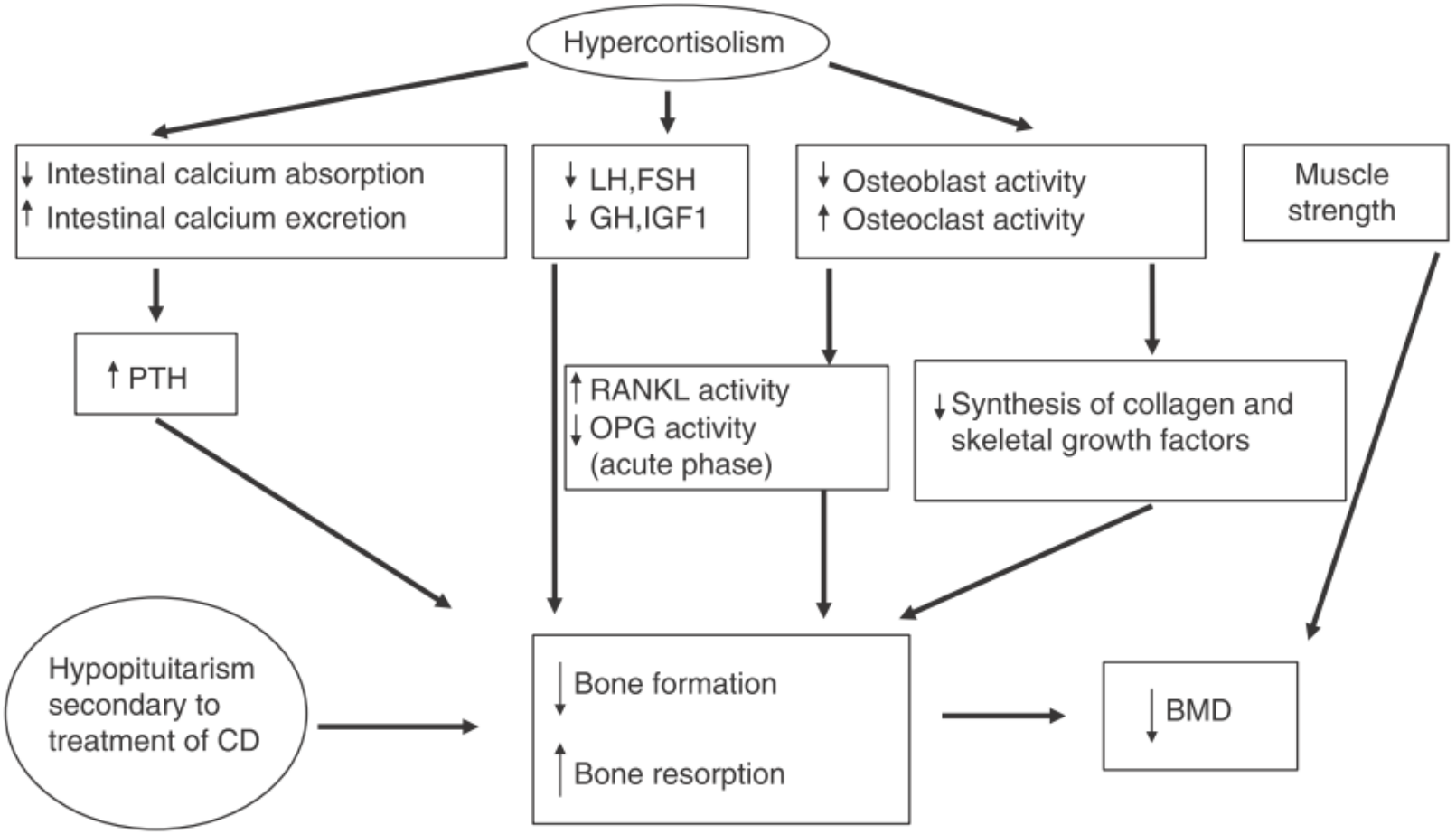


Figure 2 Pathogenesis of bone disease in CD. BMD: bone mineral density; CD: Cushing's disease; FSH: follicle-stimulating hormone; GH: growth hormone; IGF-1: insulin-like growth factor type 1; LH: luteinizing hormone; OPG: osteoprotegerin; PTH: parathyroid hormone; RANKL: receptor activator of nuclear factor-kappa B-ligand.

Skeletal involvement in adult patients with endogenous hypercortisolism

J. Endocrinol. Invest. 31: 267-276, 2008

I. Chiodini[1], M. Torlontano[2], V. Carnevale[3,4], V. Trischitta[2,5], and A. Scillitani[2]

Table 1 - *Studies evaluating bone turnover and mass in patients with Cushing'ssyndrome.*

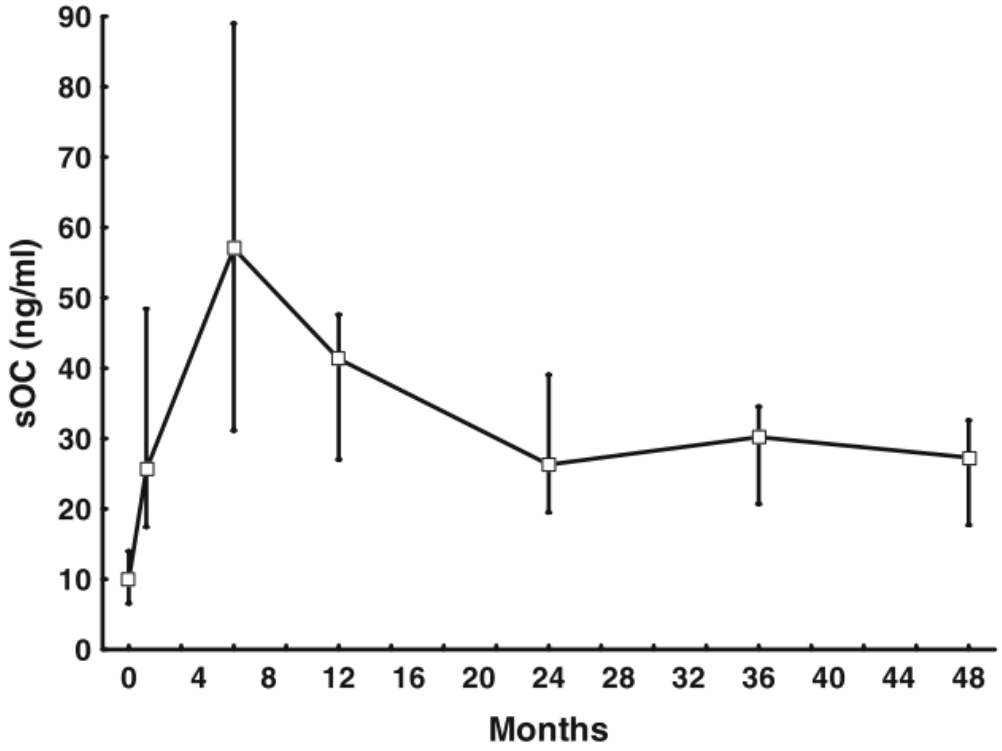
Study	Design	No.	F/M	Eug/hyp	Bone apposition			Bone resorption					Bone mass					
					BGP	ALP	PICP PINP	ICTP	HOP	DPyr	NTX	CTX	LS QCT	LS DXA	FN DXA	FA DXA	tFA QCT	QUS
Piovesan, 1994 (29)	Cross-sectional controlled	12	10/2	6/6	↓	-	↓	-	-	-	-	-	-	-	-	-	-	-
Hermus, 1995 (30)	Longitudinal intervention	20	16/4	18/2	N	N	N	N	↑	-	-	-	-	↓	↓	-	-	-
Osella, 1997 (31)	Cross-sectional controlled	18	15/3	13/5	↓	↓	N	N	-	-	-	-	-	-	-	-	-	-
Sartorio, 1998 (32)	Cross-sectional controlled	12	10/2	-	↓	-	-	↓	-	-	-	-	-	-	-	-	-	-
Chiodini, 1998 (23)	Cross-sectional controlled	18	18/0	18/0	↓	-	-	-	↑	↑	-	-	↓	↓	↓	-	↓	-
Di Somma, 1998 (33)	Longitudinal intervention	39	18/21	14/25	↓	-	-	-	-	-	↑	-	-	↓	↓	-	-	-
Godang, 1999 (34)	Cross-sectional controlled	23	17/6	-	↓	-	N	↑	-	-	-	↑	-	↓	↓	↓	-	-
Tauchmanovà, 2001 (35)	Cross-sectional controlled	34	20/14	34/0	-	N	-	-	-	-	-	-	-	↓	↓	-	-	↓
Cortet, 2001 (36)	Cross-sectional controlled	23	20/3	21/2	↓	N	N	N	-	-	-	↓	-	↓	↓	-	-	↓
Francucci, 2002 (37)	Cross-sectional controlled	15	15/0	7/8	↓	N	-	-	-	N	-	-	-	↓	↓	-	-	-
Kristo, 2002 (16)	Cross-sectional controlled	33	24/09	15/18	N	-	-	-	-	-	-	↑	-	↓	↓	↓	-	-
Di Somma, 2003 (24)	Longitudinal controlled	9	6/3	9/0	↓	-	-	-	-	-	↑	-	-	↓	-	-	-	-
Minetto, 2004 (38)	Cross-sectional controlled	38	30/8	19/11	-	-	-	-	-	-	-	-	-	↓	-	-	-	-
Karavitaki, 2004 (39)	Cross-sectional controlled	29	29/0	13/16	-	-	-	-	-	-	-	-	-	-	-	N	↓ *	-	N
Tauchmanova, 2006 (25)	Cross-sectional controlled	80	49/51	-	↓	-	-	-	↓	-	-	-	-	↓	↓	-	-	-
Kristo, 2006 (40)	Longitudinal intervention	33	24/9	18/15	↓	-	-	-	-	-	-	↑	-	↓	↓	-	-	-

F: female patients; M: male patients; Eug: eugonadal patients; Hyp: hypogonadal patients; BGP: bone Gla-protein (osteocalcin); ALP: alkaline phosphatase; PICP: carboxy-terminal propeptide of type 1 procollagen; PINP: amino-terminal propeptide of type 1 procollagen; ICTP: carboxyterminal cross-linked telopeptide of type 1 collagen; HOP: urinary hydroxyproline; DPyr: urinary deossi-pyridinoline; NTX: urinary cross-linked amino-terminal telopeptides of type 1 collagen; CTX: carboxy-terminal telopeptides of type 1 collagen; LS: lumbar spine; QCT: quantitative computed tomography; DXA: dual x-ray absorptiometry; FN: femoral neck; FA: forearm; tFA: trabecular bone at forearm; QUS: quantitative ultrasonography; N: comparable in respect to controls' levels; *in post-menopausal women.

Bone turnover in patients with endogenous Cushing's syndrome before and after successful treatment

Osteoporos Int (2010) 21:637–645

Á. Szappanos · J. Tőke · D. Lippai · A. Patócs · P. Igaz · N. Szücs · L. Fütő · E. Gláz · K. Rácz · M. Tóth



Time course of serum osteocalcin concentrations before (month 0) and after the cure of endogenous hypercortisolism (months 1 – 6 – 12 – 24 – 36 – 48)

Pituitary (2012) 15:193–201

Spontaneous recovery of bone mass after cure of endogenous hypercortisolism

Maria Elena Randazzo · Erika Grossrubatscher · Paolo Dalino Ciaramella · Angelo Vanzulli · Paola Loli

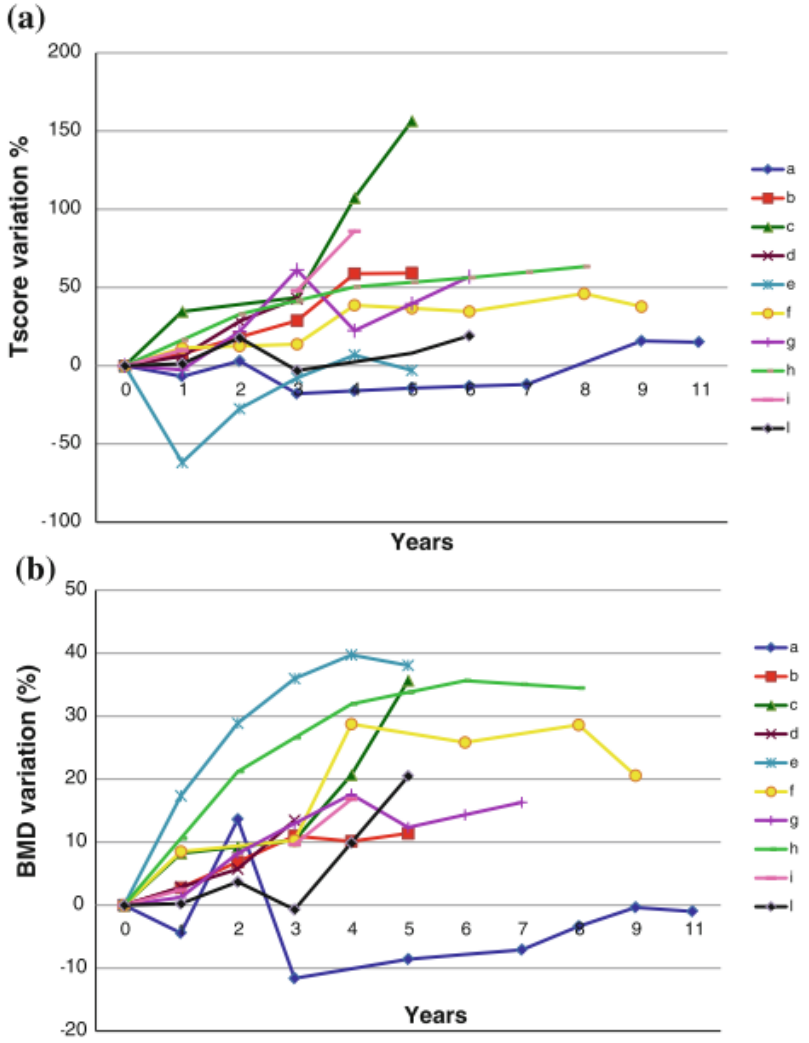


Fig. 1 **a** Variation of T score L2–L4 over time in the eleven patients followed up for a median of 7 years (long term follow up). **b** Variation of BMD L2–L4 over time in the eleven patients followed up for a median of 7 years (long term follow up)

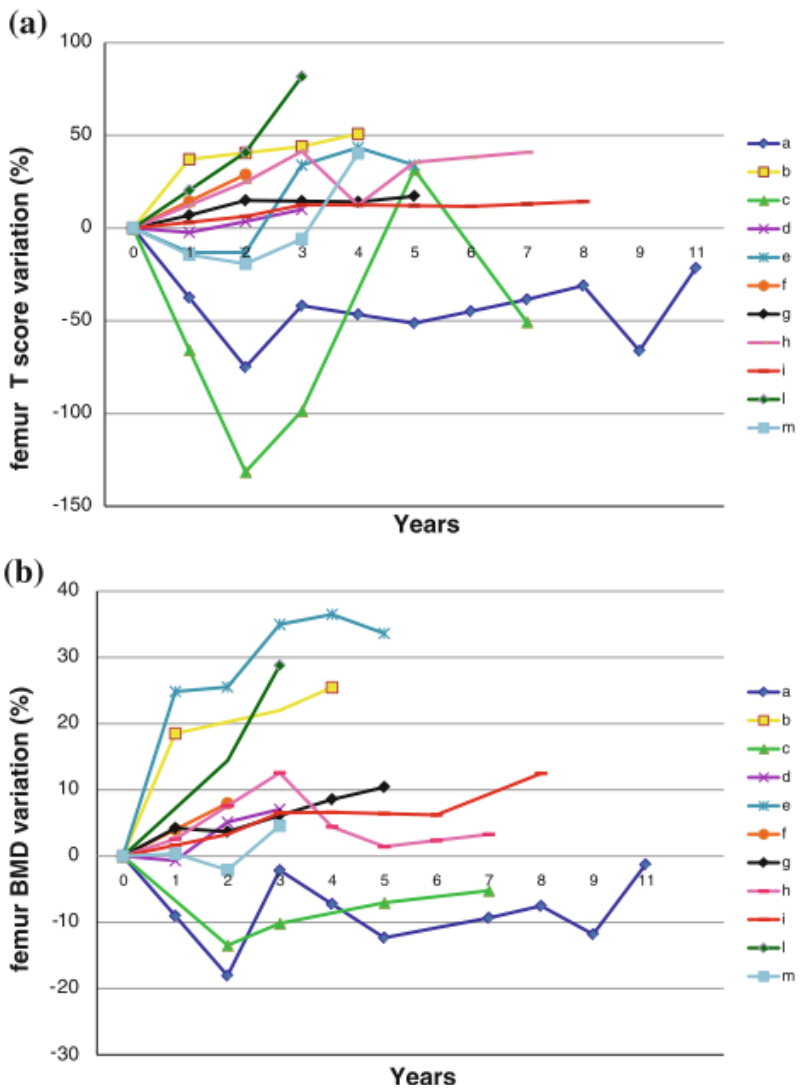


Fig. 2 **a** Variation of T score of femur neck over time in the eleven patients followed up for a median of 7 years (long term follow up). **b** Variation of BMD of femur neck over time in the eleven patients followed up for a median of 7 years (long term follow up)

JOURNAL OF BONE AND MINERAL RESEARCH
Volume 24, Number 11, 2009

Deleterious Effects of Glucocorticoid Replacement on Bone in Women After Long-Term Remission of Cushing's Syndrome

Maria-José Barahona,[1] Nuria Sucunza,[1] Eugenia Resmini,[1] Jose-Manuel Fernández-Real,[2] Wifredo Ricart,[2] Jose-Maria Moreno-Navarrete,[2] Teresa Puig,[3] Ana M. Wägner,[1] José Rodriguez-Espinosa,[1] Jordi Farrerons,[4] and Susan M. Webb[1]

TABLE 1. Comparison Between Cured and Active CS Patients and Normal Matched Controls

	Cured CS	*Active CS*	*Controls*	*p*
N	37	14	85	
Whole BMC (kg)	1.88 ± 0.31	1.79 ± 0.20	2.05 ± 0.29	0.001*
Whole BMD (g/cm^2)	1.05 ± 0.09	1.02 ± 0.06	1.11 ± 0.09	0.001*
Lumbar BMD (g/cm^2)	1.05 ± 0.18	0.92 ± 0.10	1.11 ± 0.20	<0.01†
Osteocalcin (ng/ml)	2 (2–10.6)	2 (2–15.4)	4.07 (2–14.7)	<0.01*
β-Crosslaps (ng/ml)	0.26 (0.02–0.58)	0.28 (0.03–1.05)	0.27 (0.09–1.02)	NS
Total P1NP (ng/ml)	39.8 (6.34–111)	32.7 (13.7–114)	42.4 (12.5–192)	NS
BMI (kg/m^2)	25.2 (18.7–45.5)	29.6 (23.7–34)	25.4 (19–43)	NS
Current age (yr)	50 ± 14	46 ± 12	50 ± 12	NS
Menopausal (%)	43	46	50	NS

Results are expressed as mean ± SD or median and range.
* *p* between controls and the other two groups.
† *p* between controls and active CS.
NS, not significant; BMI, body mass index.

Series with a long follow-up after remission of hypercortisolism (mean follow-up of 11 years).

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TABLE 2. Comparison Between Cured and Active CS Patients and Normal Matched Controls: Role of Estrogens

	Cured CS		*Active CS*		*Controls*			
	Estrog+	*Estrog−*	*Estrog+*	*Estrog−*	*Estrog+*	*Estrog−*	*p**	*p*†
N	20	17	6	8	43	42		
BMC (kg)	1.96 ± 0.22	1.79 ± 0.38	1.83 ± 0.26	1.76 ± 0.15	2.15 ± 0.29	1.94 ± 0.24	<0.01‡	NS
Whole BMD (g/cm^2)	1.07 ± 0.06	1.03 ± 0.11	1.05 ± 0.08	1.01 ± 0.05	1.14 ± 0.08	1.07 ± 0.09	<0.01‡	NS
Lumbar BMD (g/cm^2)	1.06 ± 0.17	1.05 ± 0.2	0.96 ± 0.08	0.89 ± 0.1	1.17 ± 0.17	1.04 ± 0.2	<0.01‡	NS

* Differences between the estrogen-sufficient groups of cured and active patients and controls.
† Differences between the estrogen-deficient groups of cured and active patients and controls.
‡ $p < 0.01$ between controls and the other two groups.
Estrog$^+$, estrogen sufficient; Estrog−, estrogen deficient.

These differences were observed in <u>estrogen-sufficient women</u> but not in those with estrogen deficiency.
This suggests that the protective effect of estrogens on bone mass is lost with hypercortisolism.

Effect of 2 years of cortisol normalization on the impaired bone mass and turnover in adolescent and adult patients with Cushing's disease: a prospective study

Clinical Endocrinology (2003) **58**, 302–308

Carolina Di Somma, Rosario Pivonello, Sandro Loche*, Antongiulio Faggiano, Michele Klain†, Marco Salvatore†, Gaetano Lombardi and Annamaria Colao

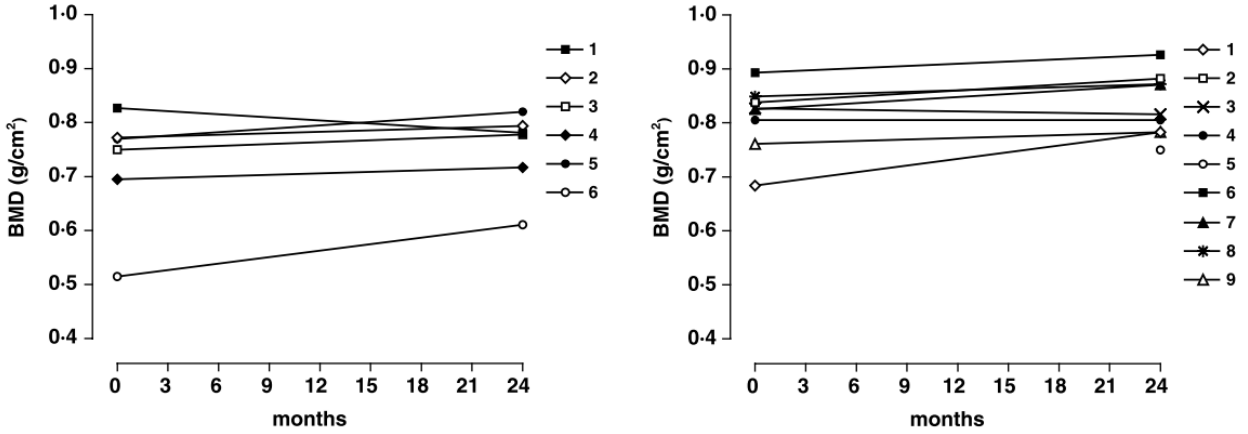


Fig. 1 Bone mineral density (BMD) at lumbar spine in adolescent (top) and adult patients (bottom) with Cushing's disease before and after 2 years of cortisol normalization.

Table 2 Hormone and bone parameters in patients, before and after disease cure, and in controls at study entry

	Young patients				Adult patients			
	Basal	2 years	Young controls	*P*	Basal	2 years	Adult controls	*P*
No.	6	6	6	–	9	9	9	–
Mean (± SEM) age (years)	15·0 ± 0·6	–	15·6 ± 0·8	0·4	41·6 ± 1·5	–	40·0 ± 2·9	–
Urinary free cortisol (μg/24 h)	865·0 ± 229·9	71·5 ± 14·8*	84·2 ± 3·5	< 0·001	977·7 ± 230·9	107·2 ± 11·3*	82·5 ± 2·5	< 0·001
Serum cortisol levels (μg/l)	330·1 ± 30·7	91·5 ± 6·8*	89·6 ± 6·7		345·2 ± 26·4	87·9 ± 9·2*	89·2 ± 5·9	
BMD lumbar spine (μg/cm²)	0·72 ± 0·04	0·76 ± 0·04*	0·98 ± 0·02‡	< 0·001	0·76 ± 0·05	0·83 ± 0·02	1·04 ± 0·02‡	< 0·001
T score lumbar spine	–	–	–		–2·41 ± 0·2	–2·22 ± 0·1*	–0·19 ± 0·2‡	< 0·001
Z score lumbar spine	–2·59 ± 0·4	–2·22 ± 0·3†	–0·16 ± 0·2‡	< 0·001	–2·12 ± 0·2	–1·87 ± 0·2*	–0·98 ± 0·2‡	< 0·001
Serum osteocalcin levels (μg/l)	1·73 ± 0·2	5·37 ± 0·5*	8·6 ± 0·2‡	< 0·001	1·58 ± 0·2	5·14 ± 0·3*	9·4 ± 3·1	< 0·001
Urinary Ntx levels (nmol BCE/mmol Cr)	159·7 ± 7·9	83·7 ± 5·7*	85·6 ± 3·3	< 0·001	125·9 ± 3·3	77·0 ± 3·2*	80·3 ± 2·8	< 0·001

Urinary free cortisol 35–135 μg/24 h; serum osteocalcin 3·0–13·0 μg/l; urinary cross-linked N-telopeptides of type I collagen (Ntx) 13–96 nmol bone collagen equivalent (BCE)/mmol creatinine in females and 23–110 nmol BCE/mmol in males. *$P < 0·01$ *vs.* basal and †$P < 0·05$ *vs.* basal at the Student *t*-test for paired data; ‡$P < 0·001$ *vs.* 2 years.

Spine Abnormalities and Damage in Patients Cured from Cushing's Disease

Pituitary 4: 153–161, 2001

Antongiulio Faggiano, Rosario Pivonello, Mariagiovanna Filippella, Carolina Di Somma, Francesco Orio Jr, Gaetano Lombardi, and Annamaria Colao

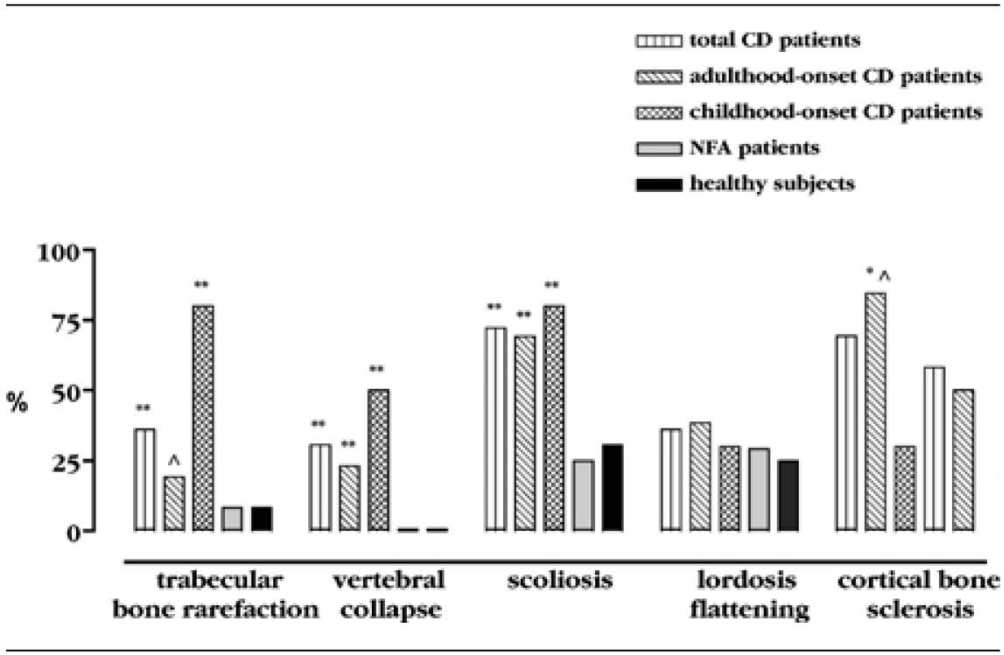


Fig. 1. *Prevalence of trabecular bone rarefaction, vertebral collapse, scoliosis, lordosis flattening and cortical bone sclerosis, at standard spine radiography in patients with Cushing's disease (CD), considered as a whole and divided i adulthood-onset and childhood-onset CD patients, in patients with nonfunctioning adenoma (NFA) and in healthy subjects (* $p < 0.05$ vs healthy subjects; ** $p < 0.05$ vs healthy subjects and NFA patients; ^ $p < 0.05$ vs childhood-onset CD patients).*

Anna Aulinas[a,*], Elena Valassi[b], Susan M. Webb[a,b]

Endocrinol Nutr. 2014;61(1):52–61

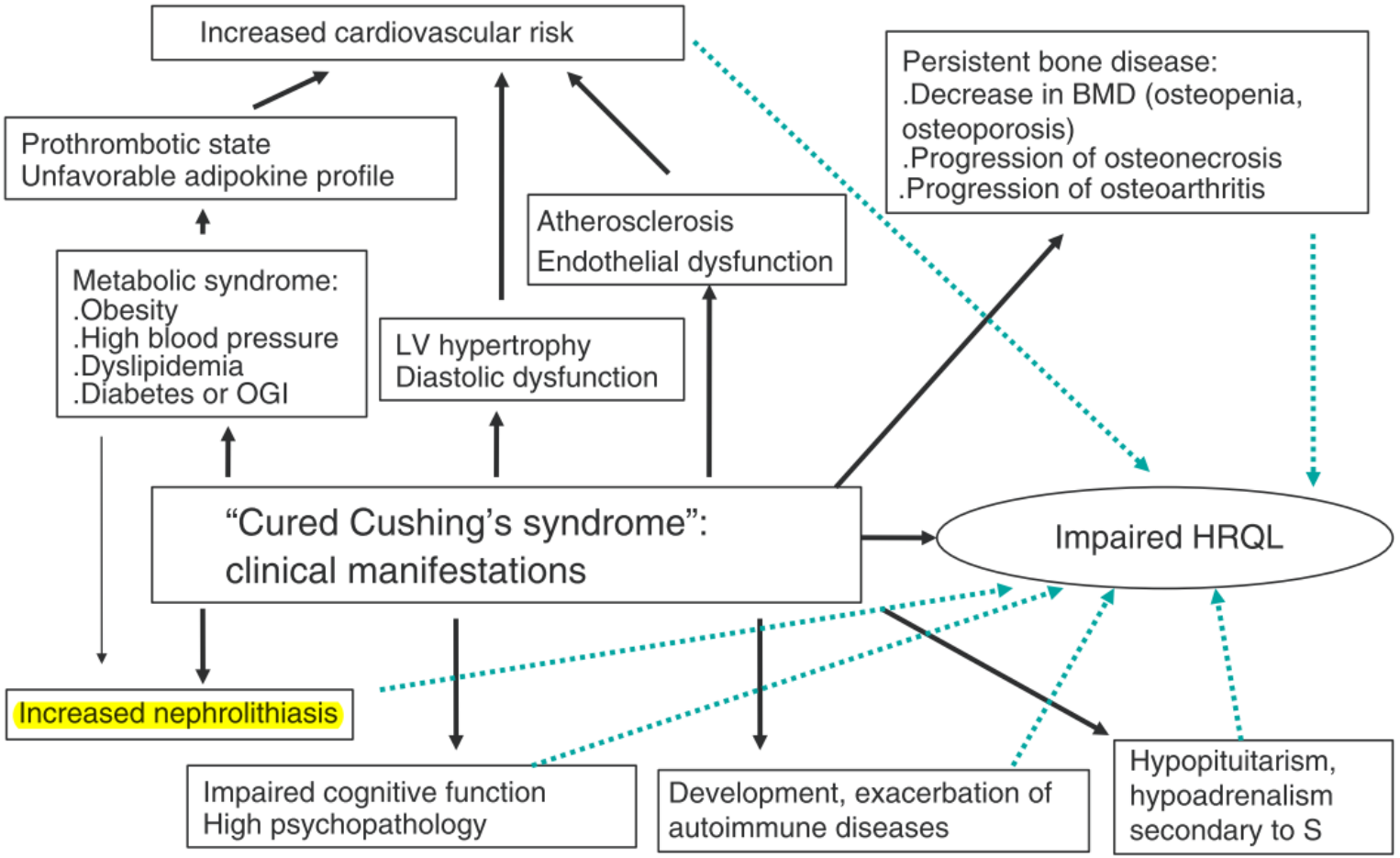


Figure 1 Schematic representation of the potential clinical manifestations and consequences despite the ''cure'' of hypercortisolism.

Nephrolithiasis in Cushing's Disease: Prevalence, Etiopathogenesis, and Modification after Disease Cure

J Clin Endocrinol Metab, May 2003, 88(5):2076–2080

ANTONGIULIO FAGGIANO, ROSARIO PIVONELLO, DANIELA MELIS,
MARIAGIOVANNA FILIPPELLA, CAROLINA DI SOMMA, MARIO PETRETTA, GAETANO LOMBARDI,
AND ANNAMARIA COLAO

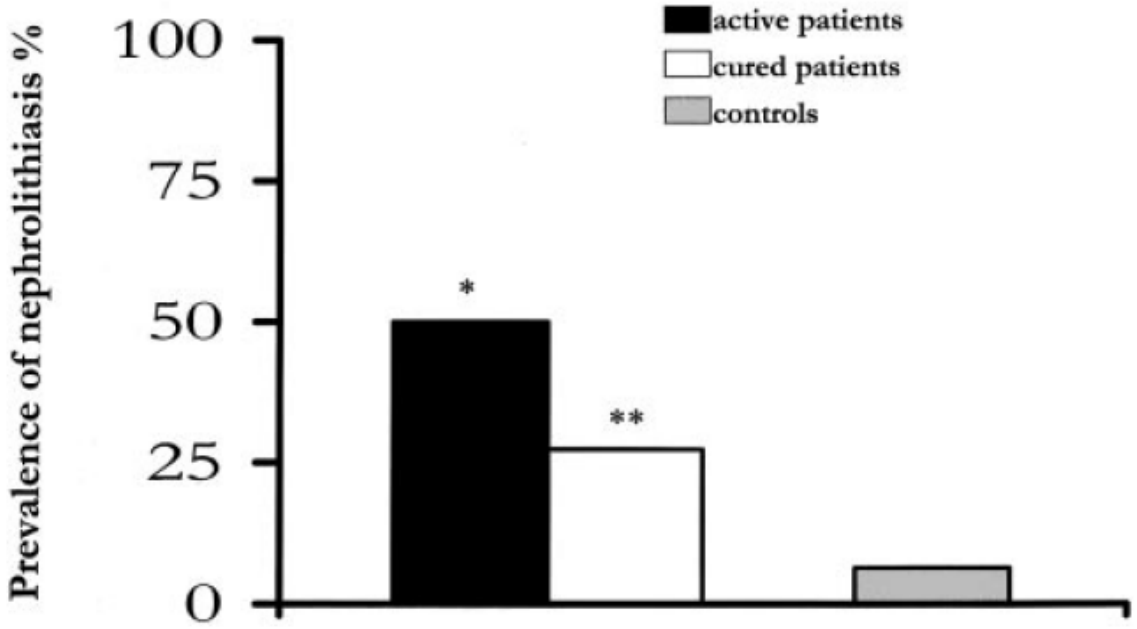


FIG. 1. Prevalence of nephrolithiasis in active and cured patients with CD and controls (*, $P < 0.001$ *vs.* controls; **, $P < 0.05$ *vs.* controls).

Nephrolithiasis in Cushing's Disease: Prevalence, Etiopathogenesis, and Modification after Disease Cure

J Clin Endocrinol Metab, May 2003, 88(5):2076–2080

ANTONGIULIO FAGGIANO, ROSARIO PIVONELLO, DANIELA MELIS,
MARIAGIOVANNA FILIPPELLA, CAROLINA DI SOMMA, MARIO PETRETTA, GAETANO LOMBARDI,
AND ANNAMARIA COLAO

TABLE 2. Frequency (%) of clinical, metabolic and urinary abnormalities based on the standard cut-off in actives and cured Cushing's disease patients and in controls

	Actives (no. 24)	Cured (no. 22)	Controls (no. 46)
Obesity/overweight	33.3/41.6[a]	13.6/36.4[a]	0/15.2
Hypertension	66.7[a]	45.4[a]	6.5
Diabetes/impaired glucose tolerance	16.6/58.3[a]	9.1/40.9[a]	0/6.5
Hypercalciuria	83.3[a,b]	4.5	2.2
Hyperuricosuria	33.3[a]	9.1	2.2
Hyperoxaluria	25	13.6	10.9
Hypocitraturia	79.2[a]	50	8.7

[a] $P < 0.01$ *vs.* controls; [b] $P < 0.01$ *vs.* cured patients.

Anna Aulinas[a,*], Elena Valassi[b], Susan M. Webb[a,b]

Endocrinol Nutr. 2014;61(1):52–61

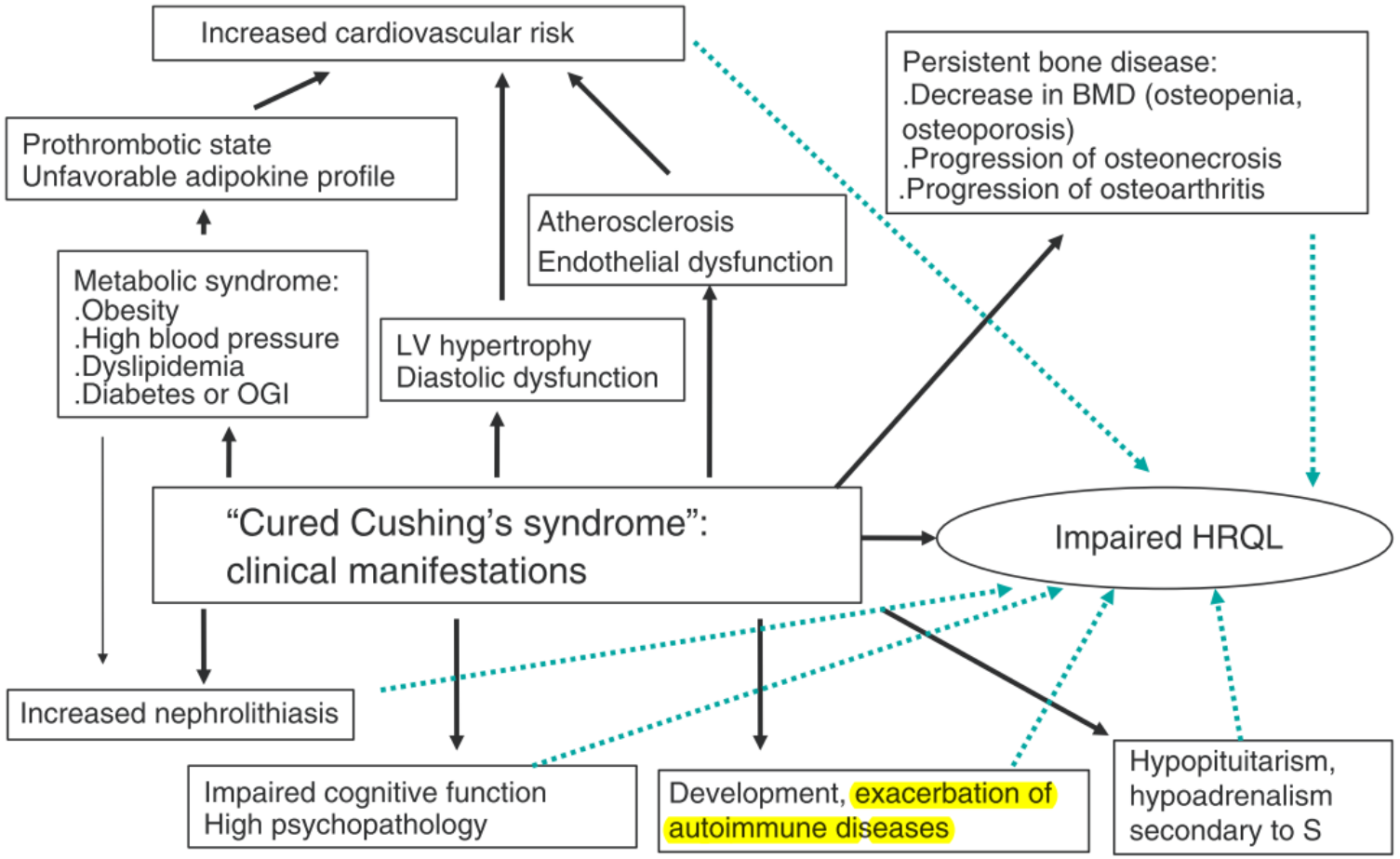


Figure 1 Schematic representation of the potential clinical manifestations and consequences despite the ''cure'' of hypercortisolism.

Journal of Steroid Biochemistry & Molecular Biology 120 (2010) 69–75

The role of the glucocorticoid receptor in inflammation and immunity☆

Ulrike Baschant, Jan Tuckermann*

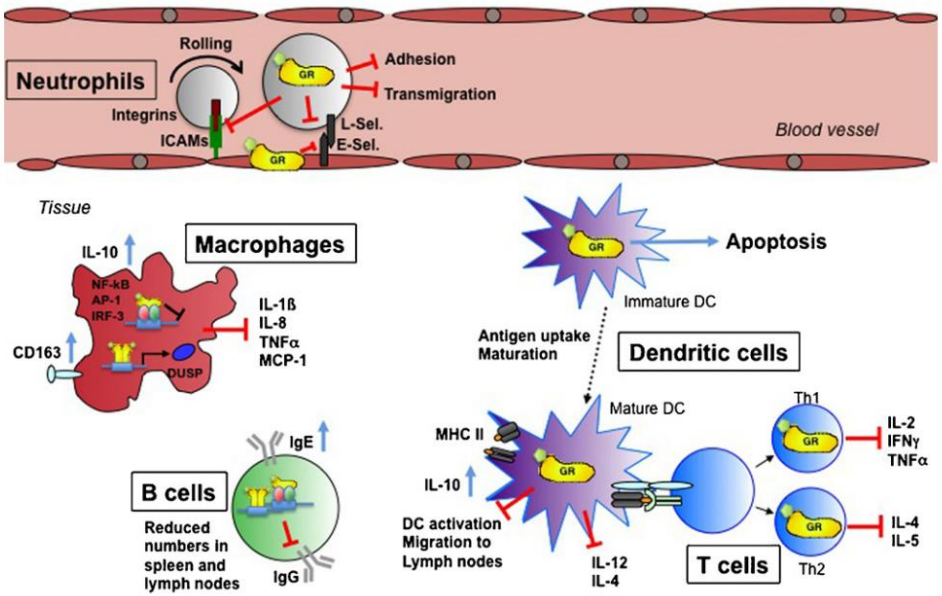


Fig. 2. Multiple effects of the GR on major immune cells. GCs influence neutrophil functions by suppressing rolling, adhesion and transmigration by reducing the expression of adhesion molecules like integrins, selectins (E-Sel., L-Sel.) and intercellular adhesion molecules (ICAMs) in neutrophils and endothelial cells. GCs efficiently suppress classical macrophage activation by induction of IL-10, an immunomodulatory cytokine and by the inhibition of the release of pro-inflammatory cytokines like TNFα, IFN-γ or IL-1β. Cytokines are suppressed by mechanisms requiring the dimerized GR (by activating GRE dependent genes like DUSP-1) as well as tethering mechanisms, i.e. interfering with NF-κB, AP-1 and IRF-3. GCs influence dendritic cells (DCs) on all levels of their life cycle. They facilitate antigen uptake of immature DCs but suppress their maturation by reduction of MHCII, co-stimulatory molecules and cytokine expression. Furthermore they potently induce apoptosis of DCs and reduce their migratory capacity. Chronic GC treatment leads to a reduction of splenic and lymph node B cell numbers, reduction of IgG production but enhanced IgE generation. T helper cell differentiation and function is affected by GCs through repression of pro-inflammatory cytokines and by regulation of transcription factors (for details see Fig. 3).

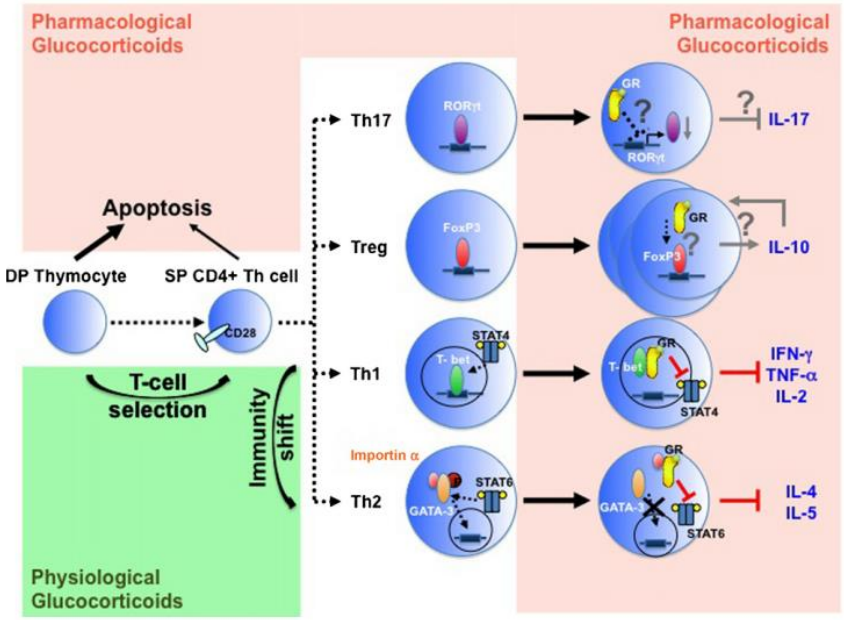
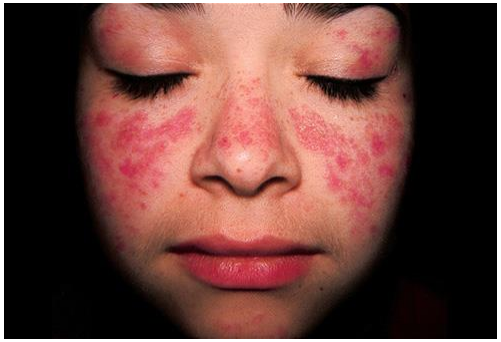


Fig. 3. Complex role of the GR in T cells. GC actions on T helper cells affect thymocyte maturation and Th cell differentiation. DP thymocytes are very sensitive towards GC-induced apoptosis, whereas SPs are less sensitive due to enhanced CD28 expression (left). At physiological doses GCs can cause a shift from Th1 response towards Th2 immunity (left below). Pharmacological doses exert anti-inflammatory effects on the different T helper cell populations by repression of pro-inflammatory cytokines and by regulation of transcription factors (right). RORγt expression is reduced by GCs in Th17 cells by an unknown mechanism. Treg numbers are increased by IL-10 released from tolerogenic myeloid cells. Whether FoxP3 is regulated by GCs is not known. In Th1 cells STAT4 and T-bet activity is inhibited by the activated GR through direct protein–protein interactions. In Th2 cells the GR prevents the nuclear import of GATA-3 and suppresses STAT6 function.

Overt Immune Dysfunction after Cushing's Syndrome Remission: A Consecutive Case Series and Review of the Literature

Filipe da Mota, Cathy Murray, and Shereen Ezzat

J Clin Endocrinol Metab, October 2011, 96(10):E1670–E1674



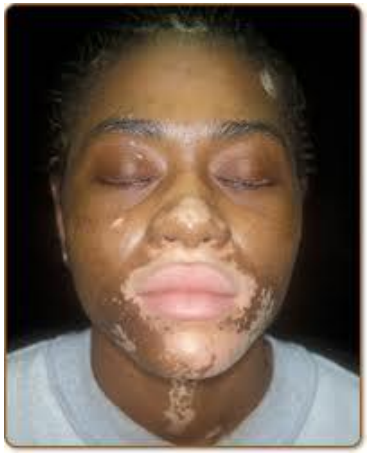
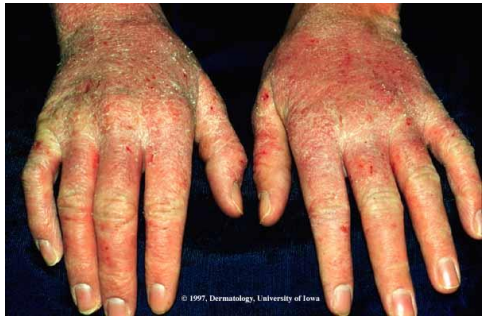
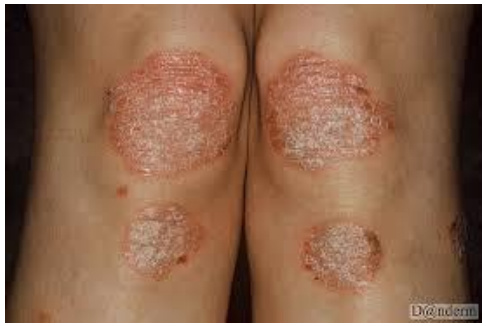


TABLE 1. First reports of specific immune dysfunctions following CS remission

Ref.	Immune dysfunction	CS etiology
2	Autoimmune thyroiditis (new onset)	Adrenal adenoma
3	Rheumatoid arthritis (exacerbation)	Pituitary adenoma
4	Celiac disease (exacerbation)	Pituitary adenoma
5	Sarcoidosis (new onset)	Adrenal adenoma
6	Systemic lupus erythematosus (new onset)	Pituitary adenoma
7	Seronegative arthritis (new onset)	Pituitary adenoma
	Retinal vasculitis (new onset)	Pituitary adenoma
8	Graves disease (exacerbation)	Ectopic
	Vitiligo, three cases (not specified)	Not specified
	Sclerosing pancreatocholangitis (new onset)	Pituitary adenoma
9	Atopic dermatitis (exacerbation)	Adrenal adenoma
	Psoriasis (exacerbation)	Pituitary adenoma
10	Autoimmune pemphigus (exacerbation)	Adrenal adenoma





Overt Immune Dysfunction after Cushing's Syndrome Remission: A Consecutive Case Series and Review of the Literature

Filipe da Mota, Cathy Murray, and Shereen Ezzat

J Clin Endocrinol Metab, October 2011, 96(10):E1670–E1674

TABLE 2. Clinical characteristics of patients with overt immune dysfunction (ID) after CS remission

Patient	Gender	Age at diagnosis of CS (yr)	Cause of CS	Treatment for CS	Urinary cortisol levels [nmol/24 h (upper limit)]		ID	Time of ID after treatment (months)	Steroid at ID onset (mg/d)
					Before CS treatment	At ID onset ± 2 months			
1	F	29	Pituitary microadenoma	2 TS, RT, K	603 (<220)	134 (<193)	Psoriasis (new onset)	36	None
2	F	25	Pituitary macroadenoma	2 TS, K, RT	1500 (<220)	196 (<220)	Psoriasis (new onset)	60	None
3	M	27	Pituitary microadenoma	TS, BA	884 (<220)	NA	Sarcoidosis (new onset)	15	Hydrocortisone (30)
4	F	45	Pulmonary neuroendocrine tumor	K, L	1610 (<330)	110 (<330)	Primary biliary cirrhosis (new onset)	4	None
5	F	58	Pituitary microadenoma	K, TS	1506 (<745)	347 (<745)	Graves Disease (new onset)	27	None
6	F	38	Pituitary microadenoma	TS	6900 (<193)	65 (<180)	Eczema (exacerbation)	6	None
7	F	34	Pituitary microadenoma	TS, K, BA	2599 (<275)	69 (<220)	Asthma (exacerbation)	1	Hydrocortisone (37.5)
8	F	38	Pituitary macroadenoma	K, 3 TS, RT, BA	308 (<220)	315 (220)	Asthma (exacerbation)	6	Hydrocortisone (35)
9	F	45	Pituitary microadenoma	K, TS	17 (<193)	NA	Generalized rash (new onset)	<1	Hydrocortisone (50)
10	F	46	Pituitary microadenoma	2 TS, K, BA	257 (<275)	714 (<275)	Rosacea-like facial skin rash (new onset)	2	Hydrocortisone (30)
11	F	32	Pituitary microadenoma	2 TS	1237 (<193)	81 (<193)	Eczematous rash over arms and back (new onset)	2	Hydrocortisone (25)

BA, Bilateral adrenalectomy; F, female; K, ketoconazole; L, lung laparoscopic surgery; NA,not available; RT, radiotherapy.

Increased prevalence of thyroid autoimmunity in patients successfully treated for Cushing's disease

Clinical Endocrinology (2000) **53,** 13–19

Annamaria Colao, Rosario Pivonello, Antongiulio Faggiano, Mariagiovanna Filippella, Diego Ferone, Carolina Di Somma, Gaetana Cerbone, Paolo Marzullo, Gianfranco Fenzi and Gaetano Lombardi

Table 2 Thyroid profile of patients with Cushing's disease (CD) before and after cure

	Serum fT3 (pmol/l)		Serum fT4 (pmol/l)		Serum TSH (mU/l)		anti-Tg titre (U/ml)		anti-TPO titre (U/ml)		Thyroid USG	
Patient	Before cure	After cure	Before cure	After cure	Before cure	After cure	Before cure	After cure	Before cure	After cure	Before cure	After cure
1.	3·7	3·5	12·1	15·4	0·6	7·2	250	790	300	685	NG	NG/T
2.	2·6	4·3	15·2	15·4	0·2	1·8	35	800	55	220	N	D
3.	3·7	4·4	15·4	12·9	0·5	2·0	26	250	38	44	NG	NG
4.	2·8	4·9	14·4	15·4	0·4	1·5	15	25	28	25	N	N
5.	5·2	2·1	16·1	8·2	0·2	9·8	190	956	215	798	NG	NG/T
6.	3·1	5·2	12·9	12·6	0·4	3·7	48	60	35	56	NG	NG
7.	4·9	3·2	8·0	9·1	0·1	1·0	12	40	18	65	NG	NG
8.	2·9	4·0	19·2	12·3	0·2	1·8	25	80	38	200	N	D
9.	4·0	3·8	19·6	16·9	0·5	1·5	55	325	71	415	N	D
10.	2·6	4·1	13·1	10·2	0·5	8·7	180	900	250	1050	NG	NG/T
11.	3·8	3·2	12·9	9·3	0·7	1·2	18	275	56	395	N	D
12.	4·6	3·5	14·8	14·0	0·4	0·5	13	27	12	35	N	N
13.	5·2	3·7	11·6	10·8	0·3	7·6	18	275	85	198	NG	NG/T
14.	3·5	3·8	14·9	19·4	0·1	1·5	28	56	47	81	N	N
15.	3·1	2·4	14·0	15·6	0·5	2·1	62	90	77	80	N	N
16.	3·4	3·8	11·2	15·7	0·6	5·9	188	350	190	544	NG	NG/T
17.	4·8	6·4	10·0	22·3	0·4	4·7	44	50	35	85	N	N
18.	4·9	2·0	22·3	8·1	0·7	20·8	26	650	15	2500	NG	NG/T
19.	3·4	3·8	17·4	15·4	0·4	8·4	65	1700	55	895	N	T
20.	3·7	3·1	14·3	12·5	0·1	3·1	25	35	18	44	N	N
Mean ±	3·8	3·8	14·5	13·6	0·4	4·7	66·0	386·7	81·9	420·7		
SEM	0·2	0·2	0·7	0·8	0·05	1·1*	16·2	99·7*	19·0	130·8*		

N, normal; NG, nodular goiter; T, thyroiditis; D, thyroid with normal size but finely nonhomogeneous pattern. Hormonal normal values, serum fT3, 2·5–5·2 pmol/L; serum fT4, 9·1–23·8 pmol/l; serum TSH, 0·5–4·7 mU/l; serum antiTg and antiTPO, 0–100 U/ml. *$P < 0·01$ compared to baseline evaluation.

Cushing's Syndrome: Aftermath of the Cure

Arq Bras Endocrinol Metab 2007;51/8

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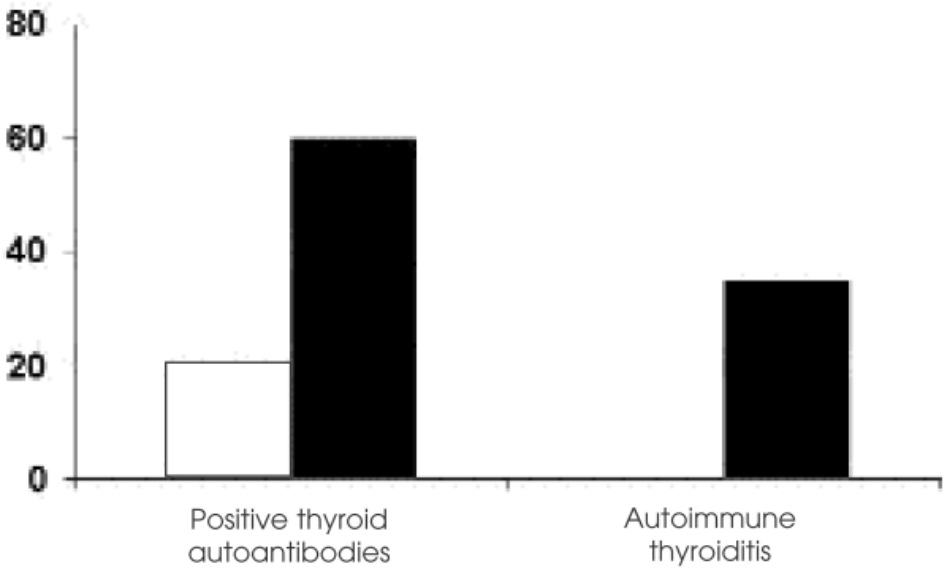

Figure 5. Prevalence of the thyroid autoimmune diseases in patients with active disease (*white bars*) and one year after disease remission (*black bars*).

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Endocrinol Nutr. 2014;61(1):52–61

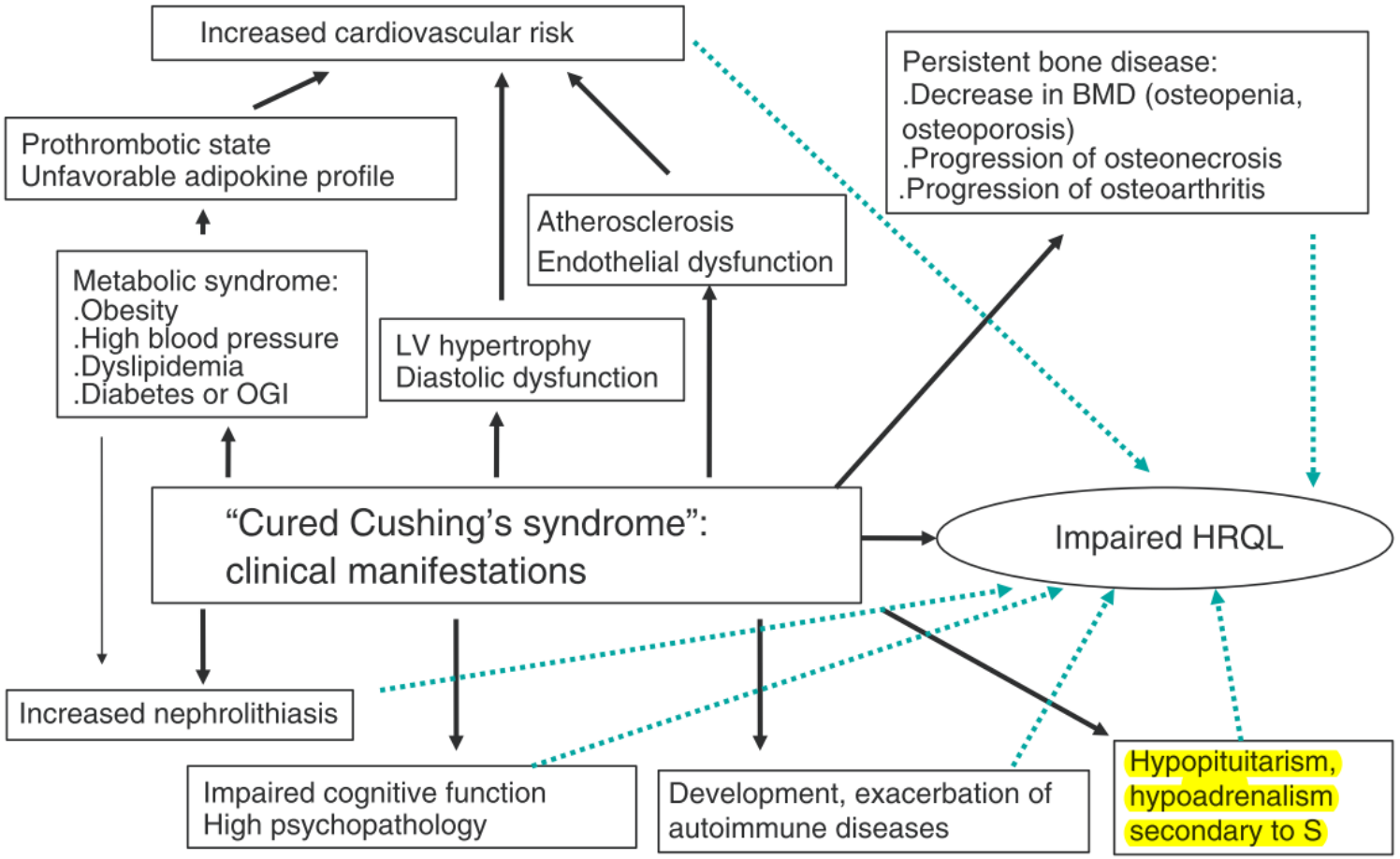
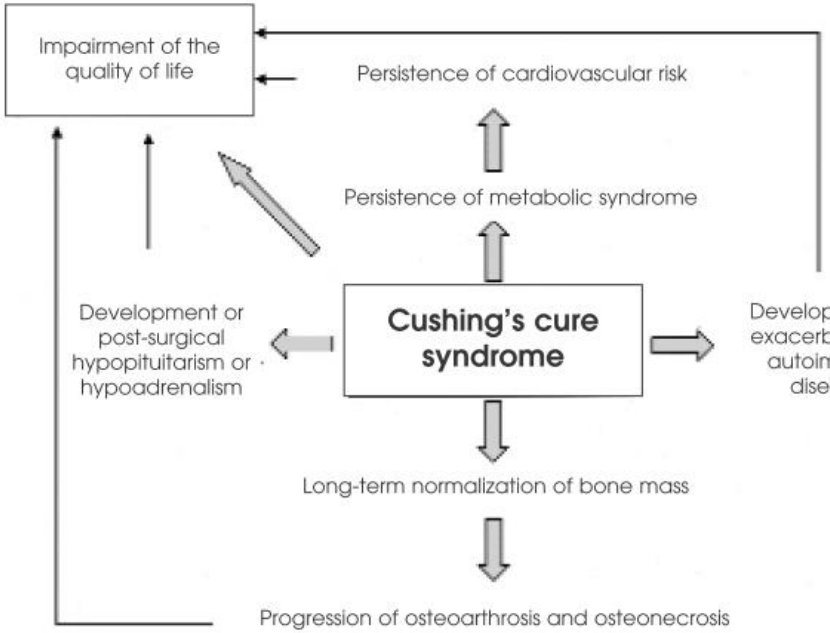


Figure 1 Schematic representation of the potential clinical manifestations and consequences despite the ''cure'' of hypercortisolism.

CONCLUSIONS



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Persistent hypercortisolism in CS is associated with a high number of several complications, only partially reversible after the remission of excess cortisol.

These findings suggest the existence of a new syndrome, which can be called "**Cushing's cure syndrome**", which is partially similar but displays some different characteristics compared to Cushing's syndrome

Advances in the epidemiology, pathogenesis, and management of Cushing's syndrome complications

J. Endocrinol. Invest. 35: 434-448, 2012

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Table 1 - *First choice medical treatment of cardiovascular complications in patients with Cushing's Syndrome.*

	Suggested therapy*
Hypertension	ACE-inhibitors; Angiotensin II receptor blockers
	MR-antagonists (if hypokalemia)
	Avoid thiazide or loop diuretics (potassium-losing effects)
Diabetes mellitus	Metformin
	DPP-4 inhibitors; GLP-1 receptor agonists
	Insulin analogs
Dyslipidemia	Statins; Fenofibrate
	Statin/ezetimibe
Coagulopathy	Antiplatelet therapy (consider in all patients with high CV risk)
	Low-molecular weight heparin; Heparin (surgery, IPS sampling)

*Based on Authors' personal experience. ACE: angiotensin-converting enzyme; MR: mineralcorticoid receptor; DPP-4: dipeptidyl peptidase-4; GLP-1: glucagon-like peptide; CV: cardiovascular; IPS: inferior petrosal sinus.

- **Bias: Influence of therapy (surgery, ketoconazole, etc); concomitant therapy (bisphosphonate, statins, etc); pituitary hormonal deficiencies and/or specific hormonal treatments; estrogen status, etc**
- **Pediatric population.**
- **Autoimmune diseases, nephrolitiasis, myopathy.**
- **Management of cured Cushing's syndrome complications: personal experience.**

Thank you for your attention