Endocrine (2018) 61:118–124
https://doi.org/10.1007/s12020-018-1524-5

ORIGINAL ARTICLE

Pasireotide treatment reduces cardiometabolic risk in Cushing's disease patients: an Italian, multicenter study

A. Albani[1] · F. Ferraù[2] · A. Ciresi[3] · R. Pivonello[4] · C. Scaroni[5] · D. Iacuaniello[4] · M. Zilio[5] · V. Guarnotta[3] · A. Alibrandi[6] · E. Messina[7] · M. Boscaro[5] · C. Giordano[3] · A. Colao[4] · S. Cannavo[2,7]

Received: 25 August 2017 / Accepted: 9 January 2018 / Published online: 30 January 2018

Abstract

Purpose Patients with Cushing's disease (CD) experience metabolic alterations leading to increased cardiovascular mortality. Recently, the visceral adiposity index (VAI) has been proposed as a marker of visceral adipose tissue dysfunction (ATD) and of the related cardiometabolic risk. We aimed to evaluate the impact of 12-month pasireotide treatment on cardiometabolic risk in CD patients.

Methods This is a multicentre, prospective, and observational study. Sixteen CD patients, referred to the Endocrine Units of the University Hospitals of Messina, Napoli, Padova, and Palermo (Italy), successfully treated with pasireotide for 12 month have been enrolled. In all patients, we assessed anthropometric, clinical, and biochemical parameters and calculated VAI, ATD severity, Framingham, and atherosclerotic cardiovascular disease (ASCVD) risk scores, before and after 6 and 12 months of treatment with pasireotide (1200–1800 mcg/daily).

Results Before starting pasireotide treatment, ATD was present in 7/16 patients (mild in 2/16, moderate in 3/16, and severe 2/16). After 12 months of treatment: (i) 24h-urinary free cortisol levels ($p = 0.003$), BMI ($p < 0.001$), waist circumference ($p = 0.001$), LDL-cholesterol ($p = 0.033$), total-cholesterol ($p = 0.032$), triglycerides ($p = 0.030$), VAI ($p = 0.015$), and ATD severity ($p = 0.026$) were significantly decreased as compared to baseline; (ii) ATD was present in only 1/16 patients; (iii) prevalence of diabetes mellitus ($p = 0.015$) and HbA1c levels ($p = 0.001$) were significantly increased as compared to baseline; (iv) Framingham and ASCVD risk scores were not significantly different from pre-treatment values.

Conclusions Twelve-month pasireotide treatment significantly reduces VAI and ATD in CD patients. These positive effects on cardiometabolic risk occur despite no change in Framingham and ASCVD risk scores and the increase in the prevalence of diabetes mellitus.

Keywords Cushing's disease · Pasireotide · Visceral adiposity index · Cardiometabolic risk · Hypercortisolism

A. Albani and F. Ferraù contributed equally to this work.

✉ F. Ferraù
francesco.ferrau1@gmail.com

[1] Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy

[2] Department of Human Pathology of Adulthood and Childhood 'G. Barresi', University of Messina, Messina, Italy

[3] Section of Endocrinology, Diabetology and Metabolism, DIBIMIS, University of Palermo, Palermo, Italy

[4] Department of Clinical Medicine and Surgery, Endocrinology Unit, University of Naples Federico II, Naples, Italy

[5] Department of Medicine (DIMED), Endocrinology Unit, University-Hospital of Padua, Padova, Italy

[6] Department of Economics, University of Messina, Messina, Italy

[7] Unit of Endocrinology, University Hospital 'G. Martino', Messina, Italy

Introduction

Cushing's disease (CD), a rare but severe condition due to an adrenocorticotropic hormone (ACTH) secreting pituitary tumor, is the most frequent cause of endogenous hypercortisolism [1]. Several studies showed that CD patients are at increased risk of mortality, especially in cases with persistent disease [2–4]. The increased mortality is mainly due to cardiovascular events as a consequence of glucocorticoid (GC)-related hypertension, structural and functional cardiovascular changes, thrombotic diathesis, and metabolic derangement [5, 6]. Indeed, GC excess induces several metabolic alterations leading to impairment of glucose tolerance, dyslipidaemia and visceral obesity, all together features of the metabolic syndrome [7]. As a consequence, in CD patients the main therapeutic goals are to normalize cortisol levels and to appropriately address the metabolic comorbidities in order to reduce the cardiovascular risk.

The first-line treatment of CD is the surgical removal of the pituitary tumor [1]. When pituitary surgery is not feasible or not curative, pharmacological control of hypercortisolism should be considered [1, 8]. Pasireotide, a multireceptor-targeted somatostatin analog, is the only pituitary directed drug approved for the treatment of CD. It has been shown to be effective in reducing urinary cortisol levels and to ameliorate the clinical picture reducing body weight and systolic (SBP) and diastolic blood pressure (DBP) and improving lipid profile and health-related quality of life [9–13].

Recently, the visceral adiposity index (VAI) has been proposed as a marker of adipose tissue distribution and dysfunction (ATD), which indirectly reflects cardiometabolic risk [14, 15]. VAI is a gender-specific mathematical model based on anthropometric and metabolic parameters [14, 15], independently associated with cardio-vascular and cerebro-vascular events as reported in several studies; it has been also proposed as early indicator of cardiometabolic risk in patients with borderline conditions, before they develop overt metabolic syndrome [14]. VAI has been proven to be a useful marker of cardiometabolic risk in patients with acromegaly and it has been shown to be a reliable measurable parameter of the positive metabolic modifications induced by cabergoline treatment in patients with prolactin secreting pituitary tumors [16, 17]. Moreover, VAI has been found to be high in patients with CS—as expected because of the GC excess related visceral adipose dysfunction—, and it has been suggested to be a potential useful index of therapeutic outcome [14, 18].

In this study, we aimed to assess the impact of 12-month therapy with pasireotide in CD patients: (i) on cardiometabolic risk, evaluated by VAI; (ii) and on cardiovascular risk, evaluated by Framingham risk score (FRS) and the 10-year primary risk of atherosclerotic cardiovascular disease (ASCVD) score according to the American College of Cardiology/American Heart Association cardiovascular risk guidelines [19].

Patients and methods

This is a multicenter, prospective, longitudinal study performed in 16 CD patients (11 females, mean age at evaluation 43.8 ± 12.1 years), referred to the Endocrine Units of the University Hospitals of Messina, Napoli, Padova, and Palermo (Italy), who underwent successful pasireotide treatment for at least 12 months.

In all patients anthropometric, clinical, and biochemical parameters were assessed and VAI, ATD severity, Framingham, and ASCVD risk scores were calculated before (baseline) and after 6 and 12 months of therapy with pasireotide (1200–1800 mcg/daily). All the parameters evaluated at 6 and 12 months have been compared with baseline findings. Moreover, the cardiometabolic indexes (VAI and ATD severity) have been correlated with clinical and biochemical parameters assessed at the three different time points (baseline, and after 6 and 12 months of treatment).

All patients had undergone pituitary surgery before starting pasireotide therapy: four of them had also received stereotactic radiotherapy completed since at least 3 years, whereas two patients had undergone unsuccessful adrenalectomy. Moreover, ten patients had undergone other medical treatments: ketoconazole in seven cases, cabergoline in six, association of cabergoline and ketoconazole had been used in two patients, and temozolomide in one patient.

In all patients pasireotide was administered at the initial dose of 600 μg twice a day (bid) subcutaneously, which was up-titrated to 900 μg bid in cases with still increased 24 h-urinary free cortisol (UFC) levels (in 1 patient after 3 months, in 1 after 6 months, in 1 after 9 months).

In all patients, concomitant pituitary deficiencies were stably replaced as appropriate (according to generally accepted criteria and to the most recent guidelines), and the biochemical evaluation of pituitary function at 6 and 12 months from enrollment ruled out the occurrence of new hormone deficits. None of the patients experienced cardiovascular events before or during treatment.

The local Ethical Committee approved the study. The patients consented to the study and signed consent form.

Anthropometric and clinical parameters

We assessed (at baseline, and after 6 and 12 months of pasireotide treatment): weight, body mass index (BMI), waist circumference, SBP and DBP, smoking habit, occurrence of diabetes mellitus (DM) or impaired glucose

Table 1 Anthropometric. clinical, and biochemical parameters before and after 6 and 12 months of treatment with pasireotide

	Baseline	After 6 months	*P*	After 12 months	*P*
Weight (kg)	89.93 ± 31.07	82.59 ± 28.29	0.001	82.06 ± 30.60	<0.001
BMI (kg/m^2)	34.43 ± 12.46	31.38 ± 10.87	0.001	31.11 ± 11.61	<0.001
Waist circumference (cm)	111.06 ± 18.67	105.87 ± 17.41	0.001	104.31 ± 19.45	0.001
SBP (mmHg)	119.68 ± 19.44	120.62 ± 13.40	NS	120.93 ± 20.10	NS
Total-cholesterol (mg/dl)	224.43 ± 47.34	201.87 ± 35.42	0.003	202.56 ± 29.17	0.032
HDL-cholesterol (mg/dl)	60.06 ± 14.48	53.81 ± 12.36	0.005	62.62 ± 15.19	NS
LDL-cholesterol (mg/dl)	138.37 ± 48.02	119.43 ± 30.30	0.014	119.75 ± 25.93	0.033
Triglycerides (mg/dl)	129.68 ± 42.83	142.81 ± 51.55	NS	101.25 ± 36.90	0.030
HbA1c%	5.87 ± 0.83	6.65 ± 1.19	0.003	6.8 ± 1.26	0.001
UFC (xULN)	2.27 ± 3.48	0.48 ± 0.30	0.001	0.64 ± 0.33	0.003
Serum cortisol (mcg/dl)	20.60 ± 8.67	15.48 ± 5.07	0.019	18.86 ± 7.66	NS
ACTH (pg/ml)	105.44 ± 118.45	70.98 ± 78.23	0.013	76.75 ± 72.52.	NS

BMI body mass index, *SBP* systolic blood pressure, *xULN* times upper limit of normal, *NS* not significant

tolerance (IGT), hypertension, dyslipidaemia, and metabolic syndrome. Diabetes mellitus or IGT have been diagnosed according to the most recent guidelines [20]. Metabolic syndrome has been diagnosed according to the NCEP-ATP III criteria [21].

Biochemical parameters

We assessed (at baseline, after 6 and 12 months of pasireotide treatment): serum cortisol level, UFC (x upper limit of normal, xULN), plasma ACTH, fasting blood glucose, glycosylated hemoglobin levels (HbA1c), and lipid profile (total and high-density and low-density lipoproteins [HDL and LDL, respectively] cholesterol levels and triglycerides [TG]). All biochemical data were obtained after overnight fasting. Glycaemia, HbA1c, ACTH, cortisol and UFC, and lipid levels were measured in the laboratories of each University Hospital by means of standard validated methods.

Cardiometabolic and cardiovascular risk assessment

VAI has been calculated in all cases by means of the proposed sex-specific algorithm in which TG and HDL-cholesterol levels are expressed in mmol/L: for males, VAI = [WC/ 39.68 × (1.88 × BMI)] x (TG/1.03) x (1.31/HDL); for females, VAI = [WC/36.58 × (1.89 × BMI)] x (TG/0.81) x (1.52/HDL) [14, 15, 22]. We distinguished patients with normal or increased VAI on the basis of the proposed age-related cut-off points of VAI [14, 22]. The ATD has been classified as absent, mild, moderate and severe, according to the age-related cut-off values of VAI, as previously proposed [14, 22].

FRS has been calculated for each patient as currently recommended (https://www.framinghamheartstudy.org/risk-functions/cardiovascular-disease/10-year-risk.php). ASCVD 10-year risk score has been calculated according to the pooled cohort risk assessment equations as elsewhere recommended [19].

Statistical analysis

The numerical data are expressed as mean and standard deviations, and the categorical variables as count and percentage. The non-parametric approach was used because the sample size is low and the numerical variables were not normally distributed, such as verified by Kolmogorov–Smirnov test. In order to evaluate the existence of statistically significant differences at two different time points (basal vs. 6 months, and vs. 12 months) the Wilcoxon test was applied for numerical parameter and the Mc Nemar test was applied for dichotomous data. The non-parametric Spearman correlation test was applied in order to assess the existence of any significant interdependence between VAI or ATD and other numerical parameters. Statistical analyses were performed using SPSS 17.0 for Window package. $P < 0.050$ two-sided was considered to be statistically significant.

Results

Anthropometric, clinical, and biochemical parameters before and after 6 and 12 months of treatment with pasireotide are summarized in Table 1.

Pasireotide therapy significantly reduced UFC levels after 6 and 12 months of treatment ($P = 0.001$ and 0.003, respectively), as well as serum cortisol and ACTH levels after 6 months ($P = 0.019$ and 0.013, respectively) (Table 1).

Table 2 Metabolic and cardiovascular comorbidities before and after 6 and 12 months of treatment with pasireotide

	Baseline	After 6 months	*P*	After 12 months	*P*
Diabetes mellitus (*n*°)	7 (43.8%)	11 (68.8%)	0.038	12 (75.0%)	0.015
Dyslipidaemia (*n*°)	8 (50.0%)	7 (43.8%)	NS	5 (31.3%)	NS
Arterial hypertension (*n*°)	9 (56.3%)	9 (56.3%)	NS	9 (56.3%)	NS

NS not significant

Table 3 Anti-diabetic therapy before and after 6 and 12 months of treatment with pasireotide

	Baseline	6 months	12 months
Patient 1	Metformin	Metformin	DPP4I
Patient 2	Metformin, insulin	Metformin, insulin, DPP4I	Metformin, insulin, DPP4I
Patient 3	–	–	Metformin
Patient 4	–	–	Metformin
Patient 5	–	–	–
Patient 6	–	Metformin	Metformin
Patient 7	Metformin	Metformin, GLP1A	Metformin, GLP1A, acarbose
Patient 8	Metformin	Metformin, GLP1A, secretagogue	Metformin, GLP1A, secretagogue
Patient 9	Metformin	Metformin, GLP1A, secretagogue	Metfromin, GLP1A, secretagogue
Patient 10	Metformin	Metformin, acarbose	Metformin, acarbose
Patient 11	Metformin	GLP1A, acarbose, insulin	Insulin, acarbose
Patient 12	–	–	–
Patient 13	–	–	–
Patient 14	–	Metformin, acarbose	Metformin, acarbose
Patient 15	Insulin	Metformin	Metformin
Patient 16	Metformin	Metformin, GLP1A, insulin	Secretagogue, GLP1A, insulin

GLP1A glucacon like pepetide 1 analog, *DPP4I* dipeptidyl peptidase 4 inhibitor

Weight, BMI and waist circumference were significantly reduced after 6 ($P = 0.001$, 0.001, and 0.001, respectively) and 12 months of therapy ($P < 0.001$, <0.001, and 0.001, respectively).

Hypertension was present at baseline, and after 6 and 12 months of treatment in nine patients (56.3%).

Dyslipidaemia was diagnosed in eight patients (50.0%) at baseline, confirmed in 7 (43.8%) after 6 months and in 5 (31.3%) after 12 months of therapy. Only one out of the eight patients with dyslipidaemia at baseline was treated with omega-3 fatty acids that have been discontinued at the 6-month evaluation. Lipid profile ameliorated since total and LDL cholesterol were significantly reduced after 6 ($P = 0.003$ and 0.014, respectively) and 12 months ($P = 0.032$ and 0.033, respectively) of treatment. A significant decrease of TG levels was found after 12 months ($P = 0.030$) (Table 1).

DM or IGT were present at baseline in 7 and 1 patients, respectively, while in 11 and 1 cases after 6 months, and in 12 and 2 patients after 12 months of pasireotide. As compared to baseline, the prevalence of DM was significantly increased at both 6-month and 12-month evaluation ($P = 0.038$ and 0.015, respectively) (Table 2). HbA1c levels were significantly increased after 6 ($P = 0.003$) and 12 months ($P = 0.001$) of pasireotide treatment. Anti-diabetic treatment during the study period is summarized in Table 3.

Metabolic syndrome was diagnosed, at baseline, in 8 (50.0%) patients (3 with ATD), while in 10 (62.5%, one with moderate ATD) after 12 months of treatment.

VAI and ATD severity were significantly reduced after 12 months of treatment ($P = 0.015$ and 0.026, respectively) as compared to baseline (Table 4). At baseline, ATD was absent in 9 cases (56.2%), mild in 2 (12.5%), moderate in 3 (18.8%), and severe in 2 (12.5%). It was absent in 8 patients (50.0%), mild in 2 (12.5%), moderate in 2 (12.5%), and severe in 4 (25.0%) after 6 months of treatment, while it was absent in 15 patients (93.7%) and moderate in 1 case (6.3%) at 12-month evaluation. No correlation was found between VAI or ATD severity and age at diagnosis, age at evaluation, smoking habit, previous medical or radio-therapy, dose of pasireotide, HbA1c, cortisol, ACTH and UFC levels, ASCVD, and FRS before or after treatment.

Mean ASCVD risk score were 4.10 ± 4.93, 6.82 ± 8.16, and 6.57 ± 8.19, while mean FRS were 11.18 ± 10.32, 10.77 ± 9.23, and 11.71 ± 10.58, at baseline and after 6 and 12 months of treatment, respectively (P = NS) (Table 4).

Table 4 Cardiometabolic and cardiovascular indexes before and after 6 and 12 months of treatment with pasireotide

	Baseline	After 6 months	*P*	After 12 months	*P*
VAI (mean ± SD)	1.93 ± 1.02	2.29 ± 1.35	NS	1.29 ± 0.67	0.015
ATD					
Absent (*n*°)	9	8	NS	15	0.026
Mild (*n*°)	2	2	–	0	–
Moderate (*n*°)	3	2	–	1	–
Severe (*n*°)	2	4	–	0	–
FRS (mean ± SD)	11.18 ± 10.32	10.77 ± 9.23	NS	11.71 ± 10.58	NS
ASCVD (mean ± SD)	4.10 ± 4.93	6.82 ± 8.16	NS	6.57 ± 8.19	NS

VAI visceral adiposity index, *ATD* adipose tissue dysfunction, *FRS* Framingham risk score, *ASCVD* atherosclerotic cardiovascular disease risk score, *SD* standard deviations, *NS* not significant

Discussion

In this study, we showed that 12-month treatment with pasireotide improved anthropometric parameters, reduced the prevalence of dyslipidaemia and ameliorated the lipid profile, and significantly reduced VAI and adipose tissue dysfunction, positively impacting on cardiometabolic risk.

It is well known that CD is associated with metabolic alterations such as impairment of glucose metabolism, dyslipidaemia, visceral obesity, and systemic arterial hypertension that configure a condition of metabolic syndrome, which in addition to cardiovascular changes and clotting disorders play a critical role in increasing cardiovascular risk and mortality rate [6, 7].

Arterial hypertension is rather common being reported in up to 80% of patients and is considered an independent predictor of mortality in CD patients [23]. In our study, the prevalence of hypertension was not affected by pasireotide treatment although normalization or decrease >50% of UFC was reached in 93.8 and 100.0% of patients after 6 and 12 months, respectively. However, the anti-hypertensive treatment was reduced in 18.8% of patients after 6 and 12 months of therapy. In the paper from Pivonello et al., decrease of UFC levels after 12 months of pasireotide treatment was accompanied by a significant improvement of SBP and DBP and, in some cases, this improvement was reached also in patients with still increased UFC levels [10].

Glucose tolerance abnormalities are among the most frequent GC excess related complications. Hyperglycemia in CD is due to several concurring factors that lead to increased peripheral insulin-resistance and gluconeogenesis, combined with reduced insulin secretion [7]. Pasireotide has been shown to be diabetogenic by reducing the secretion of both insulin and incretins [24]. However, pasireotide induced hyperglycemia can be successfully controlled by using a proper therapeutic strategy as recently suggested [25]. As expected, in our study, HbA1c levels and prevalence of DM significantly increased during pasireotide treatment. Moreover, elevation in fasting glucose also explains the slight increase in the prevalence of metabolic syndrome after 12 months of treatment.

CD patients generally show an atherogenic lipid profile, with increased LDL cholesterol and TG and reduced HDL cholesterol levels [6, 7]. In this study, lipid metabolism parameters significantly improved and, as a consequence, prevalence of dyslipidaemia decreased after 12-month treatment with pasireotide, in line with previous reports [1, 10].

Up to 100% of patients with CD has abdominal or visceral obesity that is strongly associated with cardiovascular risk [5–7]. Since waist circumference alone is not able to differentiate between visceral and subcutaneous fat mass, recently VAI has been proposed as a marker of visceral fat dysfunction, which indirectly reflects cardiometabolic risk [14, 15]. Some authors demonstrated that moderate and severe ATD are independently associated with cardiovascular events, while mild, moderate, and severe ATD with cerebrovascular events [14]. Furthermore, VAI has been shown to be a marker of an unfavorable adipokine profile, which is also frequently altered in patients with hypercortisolism [7, 26]. The relevance of VAI has been also explored in some endocrine diseases. In women with polycystic ovary syndrome, VAI correlated with severity of anovulation, insulin resistance and inflammation [27, 28]. In acromegaly, VAI seems to be strongly related to insulin resistance, ATD, and cardiometabolic risk, especially in post-menopausal women [17]. Moreover, VAI has been shown to correlate with insulin sensitivity in adult GH deficient patients and to be positively influenced by GH replacement treatment, in line with other findings suggesting a strong relationship among GH axis, VAI, and metabolic risk [29, 30]. In euthyroid type 2 diabetic subjects, higher TSH levels associated to higher VAI values and other cardiovascular risk factors [31]. In patients with prolactinoma, two studies demonstrated that cabergoline treatment reduces significantly VAI, improving metabolic profile and insulin sensitivity [16, 32]. VAI has been shown to be a reliable marker of cardiometabolic risk also in patients with craniopharyngioma [33]. In CD patients,

because of the increase in WC, BMI, and TG and lower HDL-cholesterol levels, VAI is higher than in general population. A recent study found an increased VAI in both women and men with CS, and confirmed the loss of gender-related cardiovascular protection of women when they experience an increase in visceral adipose tissue [18]. In the present study, after 12 months of pasireotide, VAI was significantly reduced as compared to baseline and ATD was absent in all patients but one. The reduction of VAI and ATD did not correlate with biochemical or clinical parameters others than lipid profile and anthropometric indexes. This could suggest that the metabolic improvement can be independent of cortisol levels decrease.

Cardiovascular risk, assessed through the calculation of Framingham and ASCVD risk scores, was not significantly different after 6 and 12 months of therapy, compared to baseline. This can be also explained on the basis of the short period of observation and of the increase in DM prevalence that significantly impact on classical cardiovascular risk score algorithms. In this regard, it is worth of noting that these scores just consider the occurrence of DM per se rather than the parameters of glycaemic control, making the VAI a more suitable marker of cardiometabolic risk in patients with CD, since their cardiovascular outcome could be more influenced by adipose tissue changes, which can persist even after remission. Moreover, the VAI could be a more appropriate parameter for cardiometabolic risk stratification even in the short-term follow-up of CD patients, since it is influenced by continuous variables differently from most of the cardiovascular risk scores' algorithms. On the other hand, a larger study population and a longer time of observation are required to definitely evaluate the impact of the combination of both pasireotide-associated reduction of VAI and diabetogenic effect on cardiovascular outcomes in CD patients. However, provided the known effects on glucose metabolism, the cardiovascular outcomes of pasireotide treatment, considering the positive impact on VAI, might be better in CD patients as compared with an other population with the same degree of glycaemic control.

In conclusion, 12-month pasireotide treatment significantly reduces VAI and ATD and consequently improves cardiometabolic risk in patients with Cushing's disease.

Funding This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Compliance with ethical standards

Conflict of interest R.P. and A.C. received unrestricted grants from Novartis; A.C. is a member of the international board for clinical trials of pasireotide in acromegaly patients; C.G. received scientific grants from Novartis and served in medical advisory boards of Novartis; S.C. received grants from Novartis and served in medical advisory boards of Novartis. The remaining authors declare that they have no conflict of interest.

References

1. R. Pivonello, M. De Leo, A. Cozzolino, A. Colao, The treatment of Cushing's disease. Endocr. Rev. **36**(4), 385–486 (2015). https://doi.org/10.1210/er.2013-1048
2. R.N. Clayton, P.W. Jones, R.C. Reulen, P.M. Stewart, Z.K. Hassan-Smith, G. Ntali, N. Karavitaki, O.M. Dekkers, A.M. Pereira, M. Bolland, I. Holdaway, J. Lindholm, Mortality in patients with Cushing's disease more than 10 years after remission: a multicentre, multinational, retrospective cohort study. Lancet Diabetes Endocrinol. **4**(7), 569–576 (2016).https://doi.org/10.1016/S2213-8587(16)30005-5
3. O.M. Dekkers, N.R. Biermasz, A.M. Pereira, F. Roelfsema, M.O. van Aken, J.H. Voormolen, J.A. Romijn, Mortality in patients treated for Cushing's disease is increased, compared with patients treated for nonfunctioning pituitary macroadenoma. J. Clin. Endocrinol. Metab. **92**(3), 976–981 (2007). https://doi.org/10.1210/jc.2006-2112
4. G. Ntali, A. Asimakopoulou, T. Siamatras, J. Komninos, D. Vassiliadi, M. Tzanela, S. Tsagarakis, A.B. Grossman, J.A. Wass, N. Karavitaki, Mortality in Cushing's syndrome: systematic analysis of a large series with prolonged follow-up. Eur. J. Endocrinol. **169**(5), 715–723 (2013). https://doi.org/10.1530/EJE-13-0569
5. R. Pivonello, M.C. De Martino, M. De Leo, C. Simeoli, A. Colao, Cushing's disease: the burden of illness. Endocrine (2016). https://doi.org/10.1007/s12020-016-0984-8
6. R. Pivonello, A.M. Isidori, M.C. De Martino, J. Newell-Price, B. M. Biller, A. Colao, Complications of Cushing's syndrome: state of the art. Lancet Diabetes Endocrinol. **4**(7), 611–629 (2016). https://doi.org/10.1016/S2213-8587(16)00086-3
7. F. Ferrau, M. Korbonits, Metabolic comorbidities in Cushing's syndrome. Eur. J. Endocrinol. **173**(4), M133–M157 (2015). https://doi.org/10.1530/EJE-15-0354
8. D. Ferone, C. Pivonello, G. Vitale, M.C. Zatelli, A. Colao, R. Pivonello, Molecular basis of pharmacological therapy in Cushing's disease. Endocrine **46**(2), 181–198 (2014). https://doi.org/10.1007/s12020-013-0098-5
9. A. Colao, S. Petersenn, J. Newell-Price, J.W. Findling, F. Gu, M. Maldonado, U. Schoenherr, D. Mills, L.R. Salgado, B.M. Biller, B.S.G. Pasireotide, A 12-month phase 3 study of pasireotide in Cushing's disease. N. Engl. J. Med **366**(10), 914–924 (2012). https://doi.org/10.1056/NEJMoa1105743
10. R. Pivonello, S. Petersenn, J. Newell-Price, J.W. Findling, F. Gu, M. Maldonado, A. Trovato, G. Hughes, L.R. Salgado, A. Lacroix, J. Schopohl, B.M. Biller, B.S.G. Pasireotide, Pasireotide treatment significantly improves clinical signs and symptoms in patients with Cushing's disease: results from a Phase III study. Clin. Endocrinol. **81**(3), 408–417 (2014). https://doi.org/10.1111/cen.12431
11. J. Schopohl, F. Gu, R. Rubens, L. Van Gaal, J. Bertherat, M. Ligueros-Saylan, A. Trovato, G. Hughes, L.R. Salgado, M. Boscaro, R. Pivonello, B.S.G. Pasireotide, Pasireotide can induce sustained decreases in urinary cortisol and provide clinical benefit in patients with Cushing's disease: results from an open-ended, open-label extension trial. Pituitary **18**(5), 604–612 (2015). https://doi.org/10.1007/s11102-014-0618-1
12. S. Petersenn, L.R. Salgado, J. Schopohl, L. Portocarrero-Ortiz, G. Arnaldi, A. Lacroix, C. Scaroni, S. Ravichandran, A. Kandra, B. M.K. Biller, Long-term treatment of Cushing's disease with pasireotide: 5-year results from an open-label extension study of a Phase III trial. Endocrine **57**(1), 156–165 (2017). https://doi.org/10.1007/s12020-017-1316-3
13. R. Pivonello, G. Arnaldi, C. Scaroni, C. Giordano, S. Cannavò, D. Iacuaniello, L. Trementino, M. Zilio, V. Guarnotta, A. Albani, A. Cozzolino, G. Michetti, M. Boscaro, A. Colao, Pasireotide

medical treatment in Cushing's disease: an Italian multicenter experience based on "real world evidence". Endocrine (2018)
14. M.C. Amato, C. Giordano, Visceral adiposity index: an indicator of adipose tissue dysfunction. Int J. Endocrinol. **2014**, 730827 (2014). https://doi.org/10.1155/2014/730827
15. M.C. Amato, C. Giordano, M. Galia, A. Criscimanna, S. Vitabile, M. Midiri, A. Galluzzo; AlkaMeSy Study, G., Visceral adiposity index: a reliable indicator of visceral fat function associated with cardiometabolic risk. Diabetes Care **33**(4), 920–922 (2010). https://doi.org/10.2337/dc09-1825
16. A. Ciresi, M.C. Amato, V. Guarnotta, F. Lo Castro, C. Giordano, Higher doses of cabergoline further improve metabolic parameters in patients with prolactinoma regardless of the degree of reduction in prolactin levels. Clin. Endocrinol. **79**(6), 845–852 (2013). https://doi.org/10.1111/cen.12204
17. A. Ciresi, M.C. Amato, G. Pizzolanti, C. Giordano Galluzzo, Visceral adiposity index is associated with insulin sensitivity and adipocytokine levels in newly diagnosed acromegalic patients. J. Clin. Endocrinol. Metab. **97**(8), 2907–2915 (2012). https://doi.org/10.1210/jc.2012-1518
18. C. Giordano, V. Guarnotta, R. Pivonello, M.C. Amato, C. Simeoli, A. Ciresi, A. Cozzolino, A. Colao, Is diabetes in Cushing's syndrome only a consequence of hypercortisolism? Eur. J. Endocrinol. **170**(2), 311–319 (2014). https://doi.org/10.1530/EJE-13-0754
19. D.C. Goff Jr., D.M. Lloyd-Jones, G. Bennett, S. Coady, R.B. D'Agostino Sr., R. Gibbons, P. Greenland, D.T. Lackland, D. Levy, C.J. O'Donnell, J.G. Robinson, J.S. Schwartz, S.T. Shero, S.C. Smith Jr., P. Sorlie, N.J. Stone, P.W. Wilson; American College of Cardiology/American Heart Association Task Force on Practice, G., 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J. Am. Coll. Cardiol. **63**(25 Pt B), 2935–2959 (2014). https://doi.org/10.1016/j.jacc.2013.11.005
20. Standards of Medical Care in Diabetes-2016, Summary of revisions. Diabetes Care **39**(Suppl 1), S4–S5 (2016). https://doi.org/10.2337/dc16-S003
21. S.M. Grundy, H.B. Brewer Jr., J.I. Cleeman, S.C. Smith Jr., C. Lenfant; American Heart, A., National Heart, L., Blood, I., Definition of metabolic syndrome: report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. Circulation **109**(3), 433–438 (2004). https://doi.org/10.1161/01.CIR.0000111245.75752.C6
22. M.C. Amato, C. Giordano, M. Pitrone, A. Galluzzo, Cut-off points of the visceral adiposity index (VAI) identifying a visceral adipose dysfunction associated with cardiometabolic risk in a Caucasian Sicilian population. Lipids Health Dis. **10**, 183 (2011). https://doi.org/10.1186/1476-511X-10-183
23. A.M. Isidori, C. Graziadio, R.M. Paragliola, A. Cozzolino, A.G. Ambrogio, A. Colao, S.M. Corsello, R. Pivonello, A.B.C.S. Group, The hypertension of Cushing's syndrome: controversies in the pathophysiology and focus on cardiovascular complications. J. Hypertens. **33**(1), 44–60 (2015). https://doi.org/10.1097/HJH.0000000000000415
24. M.G. Baroni, F. Giorgino, V. Pezzino, C. Scaroni, A. Avogaro; Italian Society for Study of, D., Italian Endocrinological, S., Italian Society for the Study of Diabetes (SID)/Italian Endocrinological Society (SIE) guidelines on the treatment of hyperglycemia in Cushing's syndrome and acromegaly. Nutr. Metab. Cardiovasc Dis. **26**(2), 85–102 (2016). https://doi.org/10.1016/j.numecd.2016.02.001
25. A. Colao, C. De Block, M.S. Gaztambide, S. Kumar, J. Seufert, F. F. Casanueva, Managing hyperglycemia in patients with Cushing's disease treated with pasireotide: medical expert recommendations. Pituitary **17**(2), 180–186 (2014). https://doi.org/10.1007/s11102-013-0483-3
26. M.C. Amato, G. Pizzolanti, V. Torregrossa, G. Misiano, S. Milano, C. Giordano, Visceral adiposity index (VAI) is predictive of an altered adipokine profile in patients with type 2 diabetes. PLoS One **9**(3), e91969 (2014). https://doi.org/10.1371/journal.pone.0091969
27. M.C. Amato, M. Verghi, A. Galluzzo, C. Giordano, The oligomenorrhoic phenotypes of polycystic ovary syndrome are characterized by a high visceral adiposity index: a likely condition of cardiometabolic risk. Hum. Reprod. **26**(6), 1486–1494 (2011). https://doi.org/10.1093/humrep/der088
28. I.I. Androulakis, E. Kandaraki, C. Christakou, A. Karachalios, E. Marinakis, T. Paterakis, E. Diamanti-Kandarakis, Visceral adiposity index (VAI) is related to the severity of anovulation and other clinical features in women with polycystic ovary syndrome. Clin. Endocrinol. **81**(3), 426–431 (2014). https://doi.org/10.1111/cen.12447
29. A. Ciresi, S. Radellini, V. Guarnotta, C. Giordano, The visceral adiposity index is associated with insulin sensitivity and IGF-I levels in adults with growth hormone deficiency. Endocrine **56**(3), 579–588 (2017). https://doi.org/10.1007/s12020-016-1076-5
30. C. Di Somma, A. Ciresi, M.C. Amato, S. Savastano, M.C. Savanelli, E. Scarano, A. Colao, C. Giordano, Alteration of the growth hormone axis, visceral fat dysfunction, and early cardiometabolic risk in adults: the role of the visceral adiposity index. Endocrine **49**(2), 492–502 (2015). https://doi.org/10.1007/s12020-014-0471-z
31. A. Giandalia, G.T. Russo, E.L. Romeo, A. Alibrandi, P. Villari, A. A. Mirto, G. Armentano, S. Benvenga, D. Cucinotta, Influence of high-normal serum TSH levels on major cardiovascular risk factors and Visceral Adiposity Index in euthyroid type 2 diabetic subjects. Endocrine **47**(1), 152–160 (2014). https://doi.org/10.1007/s12020-013-0137-2
32. R.S. Auriemma, L. Granieri, M. Galdiero, C. Simeoli, Y. Perone, P. Vitale, C. Pivonello, M. Negri, T. Mannarino, C. Giordano, M. Gasperi, A. Colao, R. Pivonello, Effect of cabergoline on metabolism in prolactinomas. Neuroendocrinology **98**(4), 299–310 (2013). https://doi.org/10.1159/000357810
33. F. Ferrau, F. Spagnolo, O.R. Cotta, L. Cannavo, A. Alibrandi, G. T. Russo, T. Aversa, F. Trimarchi, S. Cannavo, Visceral adiposity index as an indicator of cardiometabolic risk in patients treated for craniopharyngioma. Endocrine (2016). https://doi.org/10.1007/s12020-016-1196-y