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Neuropsychiatric and cardiometabolic comorbidities in patients with previously diagnosed Cushing's disease: a longitudinal observational study.

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Abstract

INTRODUCTION. Only few studies have systematically investigated neuropsychiatric aspects in patients with Cushing's disease (CD). Pain syndromes have been described to exist in patients with pituitary adenomas, but so far no systematical investigation has been conducted in patients with CD. Additionally, CD has an association with cardiometabolic comorbidities which ultimately leads to increased morbidity and mortality. Long-term treatment of the hypercortisolic state cannot prevent persistence of an unfavorable cardiometabolic risk profile. Finally, chronic hypercortisolism is known to impact the health-related quality of life (HRQoL).

We aim to systematically investigate the neuropsychiatric- and cardiometabolic comorbidities, as well as assess the HRQoL, in patients with previously diagnosed CD in a longitudinal fashion.

METHODS AND ANALYSIS. In this longitudinal study, we will assess 20 CD patients displaying biochemical control 24 months after recruitment in the initial cross-sectional study (n=80). Patients after surgical, before/under/after radiological and/or under current medical treatment will be included. Primary outcomes include changes in mean urinary free cortisol and changes in specific pain patterns. Secondary/exploratory neuropsychiatric domains include depression, anxiety, personality, sleep, body image and quality of life. Secondary/exploratory cardiometabolic domains include anthropometric parameters, cardiometabolic risk biomarkers and insulin resistance. Additional domains will be investigated if warranted by clinical indication. Safety assessment under medical therapy will include liver enzymes, ECG abnormalities and hyperglycemia.

ETHICS AND DISSEMINATION. Risk of damage from study-conditioned measures is very small and considered ethically justified. Dual X-ray Absorptiometry (DXA) may call for detailed fracture risk assessment. However, the radiation dose is very small and only administered on clinical indication, therefore considered ethically justified.

This protocol has been approved by the local medical ethics committee.

Introduction

Clinical presentation of Cushing's disease (CD) reflects chronic cortisol excess and comprises a broad spectrum of features, amongst others psychiatric disorders such as depression and psychosis (1). Despite these clinical observations, only few studies have investigated systematically and with standardised instruments neuropsychiatric aspects in patients with CD such as psychopathology (2), neuropsychology (3), personality, sleep, pain, brain architecture (4) and quality of life (5;6) and how these comorbidities and symptoms are affected by different therapy regimens. Moreover, it is known that patients with pituitary adenomas frequently suffer from pain syndromes e.g. headache (7), however this has not been systematically investigated in a subset of CD-patients to date. This is the main reason for selecting the change in pain patterns as a primary endpoint in this study.

Furthermore, CD is associated with increased morbidity and mortality, mostly due to cardiometabolic comorbidities such as arterial hypertension, glucose intolerance, diabetes mellitus, dyslipidaemia, thromboembolic complications as well as a hypercoagulable state.(8-10) Treatment of hypercortisolism has been demonstrated to be associated with a significant reduction in mortality and morbidity. However, even after long-term cure of the disease (mean time of hormonal cure 11±6 years), patients exhibit a persistent accumulation of central fat comparable to active hypercortisolism, leading to a persistent and unfavourable cardiometabolic risk profile (11).

Chronic exposure to hypercortisolism has a significant impact on patient's health and health-related quality of life (HRQoL), as demonstrated with generic questionnaires. Two disease-generated questionnaires, the CushingQoL and the Tuebingen CD-25, have been developed in order to evaluate HRQoL in patients with CD (6;12). Interestingly, even after long-term remission of CD (duration of remission 13.3 ± 10.4 years), impaired quality of life persists as a remaining effect of long-standing hypercortisolism(13).

The aim of this study is to systematically assess neuropsychiatric- and cardiometabolic comorbidities, as well as HRQoL, in CD patients displaying biochemical control 24 months after recruitment in the initial cross-sectional study in order to scientifically verify clinical observations. This addresses a hiatus in our current understanding of CD and may ultimately lead to better patient-management.

Conclusions cross-sectional study

Our research group has assessed 80 patients with CD in a cross-sectional setting. Results indicate that in a cross-sectional observational study: patients with CD a.o. demonstrated to have a particular high susceptibility to pain (Dimopoulou et al, submitted for publication May 2014, under revision EJE) and increased anxiety-associated personality traits.(14) This study will expand on these previous findings.

Method

Study population

Only few clinical data regarding the development/improvement of neuropsychiatric comorbidities in patients with CD under treatment exist. Therefore, in order to determine the appropriate sample size we cannot make use of any well-known or estimated variances or mean value differences of the target variables.

To determine the sample sizes that are needed to detect a difference between two proportions, a priori power calculation has been conducted. Hereby, the expected proportion of mental disorders/pain syndromes in the study sample has been based on the above mentioned references. Specifying Type I error as 0.05 and a power ≥80%, (δ=42, σ=28) a sample size of ±14 patients will be needed to detect the specified differences. Assuming a safe margin, we deem 20 patients to more than sufficient for our study-targets.

Following previous rationale, we will recruit 20 (of the initial 80 patients enrolled in the cross-sectional part of the study) patients with previously diagnosed CD, who will show biochemical control of the disease 24 months after study enrolment, including patients after surgical, before/under/after radiological and/or under current medical treatment. Patients will be recruited from the Endocrine Outpatient Clinic of the Max Planck Institute of Psychiatry, Munich and the Department of Internal Medicine, Ludwig-Maximilians-University, Munich.

Inclusion criteria include:

1. Adult patients with confirmed CD, who will show biochemical control of the disease 24 months after initial study enrolment including patients after surgical, before/under/after radiological and/or under current medical treatment.
2. Written informed consent.

Exclusion criteria include:

1. Female pregnant patients.

Primary objectives

In order to document arithmetic and percentual change in mean urinary free cortisol (UFC) values between uncontrolled state/before treatment (baseline) versus biochemical control of CD (2-years follow-up), we will measure the mean of absolute changes in UFC values in both groups.

In order to document arithmetic and percentual change in specific pain patterns between uncontrolled state/before treatment (baseline) versus biochemical control of CD (2-years follow-up), we will measure the change in painDETECT scores.

Secondary/exploratory

In order to document the change in neuropsychiatric comorbidities between uncontrolled/before treatment (baseline) versus biochemical control of CD (2-years follow-up), we assess the following domains with the associated standardized questionnaires:

- Depression using Beck's Depression Inventory (BDI).
- Anxiety using State-Trait Anxiety Inventory (STAI).
- Personality using Cloninger Temperament and Personality Questionnaire (TPQ) and Eysenck Personality Questionnaire (EPQ-RK).
- Daytime sleepiness using Epworh Sleepiness Scale (ESS).
- Subjective sleep using Pittsburgh Sleep Quality Index (PSQI).
- Specific pain patterns using Migraine Disability Assessment (MIDAS) and German Society for the Study of Pain (DGSS).
- Body image using Fragebogen zur Beurteilung des eigenen Körpers (FBeK) and Fragebogen zum Körperbild (FKB-20).
- HRQoL using SF-36, EuroQoL and CushingQoL.
- Sleep EEG, cognition and functional connectivity (MRI) (only in patients with a clinical indication e.g. severe cognitive impairment or severe sleep disorder).

In order to document the change in cardiometabolic comorbidities between uncontrolled/before treatment (baseline) versus biochemical control of CD (2-years follow-up), we will assess the following domains:

- Anthropometric parameters including height, weight, body mass index (BMI), waist- and hip circumference and waist-to-height-ratio.

- Cardiometabolic risk biomarkers including fasting plasma glucose, glycosylated haemoglobin (HbA1c), triglycerides, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL) and lipoprotein(a).
- Insulin resistance using HOMA index.
- Bone mineral density, fat-free mass, fat mass and fat mass percentage using dual-energy X-ray absorptiometry (DXA) (only in patients with clinical indication e.g. markedly elevated fracture risk, postmenopausal women before initiation of hormonal replacement therapy, hypogonadism, familial osteoporosis, primary hyperparathyroidism or long-term glucocorticoid therapy).

Safety

To assess the safety of current medical treatment for CD, we will report all adverse- and serious adverse advents under treatment with severity graded according to the Common Toxicity Criteria for Adverse Events (CTCAE) version 3.0. If CTCAE grading does not exist, Common Toxicity Criteria (CTC) grades 1-4, will be used (higher scores indicating greater severity).

Assessment of safety under current medical treatment will include:

- Assessment of liver enzymes (ALT, AST, ALP and total bilirubin).
- Assessment of ECG abnormalities (QTcF interval).
- Assessment of hyperglycemia (fasting plasma, glucose, insulin, HbA1c).

Current medical treatment will be discontinued if:

- ALT or AST > 3xULN and total bilirubin ≥ 2xULN and ALP < 2xULN.
- ALT or AST > 5xULN and ≤ 8xULN persistent for more than 2 weeks.
- ALT or AST 8xULN.
- QTcF > 480 msec.
- Uncontrolled diabetes mellitus.

Ethics and dissemination

This is a longitudinal observational study. All patients will provide their written informed consent which can be withdrawn at any time during study participation.

The risk for study participants to suffer damage from study-conditioned measures is very small and from the sponsor's point of view ethically justified.

Recent guidelines underline the importance of detailed fracture risk assessment in patients with CD by assessment of bone mineral density by dual X-ray absorptiometry (DXA) (15). The amount of radiation used is extremely small and therefore, according to our opinion, ethically justified.

This protocol has been approved by the local medical ethics committee.

Author's contributions

Christina Dimopoulou and Victor Geraedts wrote the clinical study protocol. Günter Karl Stalla and Caroline Sievers were responsible for the design of the study, the inclusion of patients and the preparation of the study protocol.

Funding statement

This work was supported by Novartis, NCC-Code: CSOM230BDE05T.

Novartis had no role in the study-design and will not have any role in the study execution, analysis- and interpretation of the data or decision to submit for publication.

Competing interests

We have read and understood BMJ policy on declaration of interests and declare no competing interests.

Reference List

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(2) Dorn LD, Burgess ES, Friedman TC, Dubbert B, Gold PW, Chrousos GP. The longitudinal course of psychopathology in Cushing's syndrome after correction of hypercortisolism. J Clin Endocrinol Metab 1997 Mar;82(3):912-9.

(3) Forget H, Lacroix A, Cohen H. Persistent cognitive impairment following surgical treatment of Cushing's syndrome. Psychoneuroendocrinology 2002 Apr;27(3):367-83.

(4) Bourdeau I, Bard C, Noel B, Leclerc I, Cordeau MP, Belair M, et al. Loss of brain volume in endogenous Cushing's syndrome and its reversibility after correction of hypercortisolism. J Clin Endocrinol Metab 2002 May;87(5):1949-54.

(5) van Aken MO, Pereira AM, Biermasz NR, van Thiel SW, Hoftijzer HC, Smit JW, et al. Quality of life in patients after long-term biochemical cure of Cushing's disease. J Clin Endocrinol Metab 2005 Jun;90(6):3279-86.

(6) Webb SM, Badia X, Barahona MJ, Colao A, Strasburger CJ, Tabarin A, et al. Evaluation of health-related quality of life in patients with Cushing's syndrome with a new questionnaire. Eur J Endocrinol 2008 May;158(5):623-30.

(7) Levy MJ, Matharu MS, Meeran K, Powell M, Goadsby PJ. The clinical characteristics of headache in patients with pituitary tumours. Brain 2005 Aug;128(Pt 8):1921-30.

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(9) Mancini T, Kola B, Mantero F, Boscaro M, Arnaldi G. High cardiovascular risk in patients with Cushing's syndrome according to 1999 WHO/ISH guidelines. Clin Endocrinol (Oxf) 2004 Dec;61(6):768-77.

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(14) Dimopoulou C, Ising M, Pfister H, Schopohl J, Stalla GK, Sievers C. Increased prevalence of anxiety-associated personality traits in patients with Cushing's disease: a cross-sectional study. Neuroendocrinology 2013;97(2):139-45.

(15) Lekamwasam S, Adachi JD, Agnusdei D, Bilezikian J, Boonen S, Borgstrom F, et al. A framework for the development of guidelines for the management of glucocorticoid-induced osteoporosis. Osteoporos Int 2012 Sep;23(9):2257-76.

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We aim to systematically investigate the neuropsychiatric- and cardiometabolic comorbidities, as well as assess the HRQoL, in patients with previously diagnosed CD in a longitudinal fashion.

METHODS AND ANALYSIS. In this longitudinal study, we will assess 20 CD patients displaying biochemical control 24 months after recruitment in the initial cross-sectional study (n=80). Patients after surgical, before/under/after irradiation therapy and/or under current medical treatment will be included. Primary outcomes include changes in mean urinary free cortisol and changes in specific pain patterns. Secondary/exploratory neuropsychiatric domains include depression, anxiety, personality, sleep, body image and quality of life. Secondary/exploratory cardiometabolic domains include anthropometric parameters, cardiometabolic risk biomarkers and insulin resistance. Additional domains will be investigated if warranted by clinical indication. Safety assessment under medical therapy will include liver enzymes, ECG abnormalities and hyperglycemia.

ETHICS AND DISSEMINATION. Risk of damage from study-conditioned measures is very small and considered ethically justified. Dual X-ray Absorptiometry (DXA) may call for detailed fracture risk assessment. However, the radiation dose is very small and only administered on clinical indication, therefore considered ethically justified.
This protocol has been approved by the local medical ethics committee.

Introduction

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Furthermore, CD is associated with increased morbidity and mortality, mostly due to cardiometabolic comorbidities such as arterial hypertension, glucose intolerance, diabetes mellitus, dyslipidaemia, thromboembolic complications as well as a hypercoagulable state (10-12) Treatment of hypercortisolism has been demonstrated to be associated with a significant reduction in mortality and morbidity. However, even after long-term cure of the disease (mean time of hormonal cure 11±6 years), patients exhibit a persistent accumulation of central fat comparable to active hypercortisolism, leading to a persistent and unfavourable cardiometabolic risk profile (13).

Chronic exposure to hypercortisolism has a significant impact on patient's health and health-related quality of life (HRQoL), as demonstrated with generic questionnaires. Two disease-generated questionnaires, the CushingQoL and the Tuebingen CD-25, have been developed in order to evaluate HRQoL in patients with CD (6; 14-15). Interestingly, even after long-term remission of CD (duration of remission 13.3 ± 10.4 years), impaired quality of life persists as a remaining effect of long-standing hypercortisolism(16).

The aim of this study is to systematically assess neuropsychiatric- and cardiometabolic comorbidities, as well as HRQoL, in CD patients displaying biochemical control 24 months after recruitment in the initial cross-sectional study in order to scientifically verify clinical observations. This addresses a hiatus in our current understanding of CD and may ultimately lead to better patient-management.

Conclusions cross-sectional study

Our research group has assessed 80 patients with CD in a cross-sectional setting. Results indicate that in a cross-sectional observational study: patients with CD demonstrated to have a particular high susceptibility to pain (17) and increased anxiety-associated personality traits.(18) This study will expand on these previous findings.

Method

Study population

Only few clinical data regarding the development/improvement of neuropsychiatric comorbidities in patients with CD under treatment exist. Therefore, in order to determine the appropriate sample size we cannot make use of any well-known or estimated variances or mean value differences of the target variables.

To determine the sample sizes that are needed to detect a difference between two proportions, a priori power calculation has been conducted. Hereby, the expected proportion of mental

disorders/pain syndromes in the study sample has been based on the above mentioned references. Specifying Type I error as 0.05 and a power ≥80%, (δ=42, σ=28) a sample size of ±14 patients will be needed to detect the specified differences. Assuming a safe margin, we deem 20 patients to be more than sufficient for our study-targets.

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Inclusion criteria include:

1. Adult patients with confirmed CD, who will show biochemical control of the disease 24 months after initial study enrolment including patients after surgical, before/under/after irradiation therapy and/or under current medical treatment.
2. Written informed consent.

Exclusion criteria include:

1. Female pregnant patients.

Primary objectives

In order to document arithmetic and percentual change in mean urinary free cortisol (UFC) values between uncontrolled state/before treatment (baseline) versus biochemical control of CD (2-years follow-up), we will measure the mean of absolute changes in UFC values in both groups.

In order to document arithmetic and percentual change in specific pain patterns between uncontrolled state/before treatment (baseline) versus biochemical control of CD (2-years follow-up), we will measure the change in painDETECT scores.

Secondary/exploratory

In order to document the change in neuropsychiatric comorbidities between uncontrolled/before treatment (baseline) versus biochemical control of CD (2-years follow-up), we assess the following domains with the associated standardized questionnaires:

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- Body image using Fragebogen zur Beurteilung des eigenen Körpers (FBeK) and Fragebogen zum Körperbild (FKB-20).
- HRQoL using SF-36, EuroQoL and CushingQoL.
- Sleep EEG, cognition and functional connectivity (MRI) (only in patients with a clinical indication e.g. severe cognitive impairment or severe sleep disorder as set in the former cross-sectional part of the study).

In order to document the change in cardiometabolic comorbidities between uncontrolled/before treatment (baseline) versus biochemical control of CD (2-years follow-up), we will assess the following domains:

- Anthropometric parameters including height, weight, body mass index (BMI), waist- and hip circumference and waist-to-height-ratio.
- Cardiometabolic risk biomarkers including fasting plasma glucose, glycosylated haemoglobin (HbA1c), triglycerides, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL) and lipoprotein(a).
- Insulin resistance using HOMA index.
  Bone mineral density, fat-free mass, fat mass and fat mass percentage using dual-energy X-ray absorptiometry (DXA) In addition, fracture risk assessment within the study population will be carried out with the FRAX algorithm (http://www.shef.ac.uk/FRAX) as suggested by *Trementino et al. 2014* (19).
- *Safety*

To assess the safety of current medical treatment for CD, we will report all adverse- and serious adverse advents under treatment with severity graded according to the Common Toxicity Criteria for Adverse Events (CTCAE) version 3.0. If CTCAE grading does not exist, Common Toxicity Criteria (CTC) grades 1-4, will be used (higher scores indicating greater severity).

Assessment of safety under current medical treatment will include:

- Assessment of liver enzymes (ALT, AST, ALP and total bilirubin).
- Assessment of ECG abnormalities (QTcF interval).
- Assessment of hyperglycemia (fasting plasma, glucose, insulin, HbA1c).

Current medical treatment will be discontinued if:

- ALT or AST > 3xULN and total bilirubin ≥ 2xULN and ALP < 2xULN.
- ALT or AST > 5xULN and ≤ 8xULN persistent for more than 2 weeks.
- ALT or AST 8xULN.
- QTcF > 480 msec.
- Uncontrolled diabetes mellitus.

Ethics and dissemination

This is a longitudinal observational study. All patients will provide their written informed consent which can be withdrawn at any time during study participation.

The risk for study participants to suffer damage from study-conditioned measures is very small and from the sponsor's point of view ethically justified.At the moment, there are no available guidelines for the management of osteoporosis induced by endogenous hypercortisolism. Within this study, bone mineral density will be measured by dual X-ray absorptiometry (DXA) and fracture risk will be assessed the FRAX algorithm, according to recently published expert opinions and suggestions (20-22). The amount of radiation used in DXA is extremely small and therefore, according to our opinion, ethically justified.

This protocol has been approved by the local medical ethics committee.

Author's contributions

Christina Dimopoulou and Victor Geraedts wrote the clinical study protocol. Günter Karl Stalla and Caroline Sievers were responsible for the design of the study, the inclusion of patients and the preparation of the study protocol.

Funding statement
This work was supported by Novartis, NCC-Code: CSOM230BDE05T.
Novartis had no role in the study-design and will not have any role in the study execution, analysis- and interpretation of the data or decision to submit for publication.

Competing interests
We have read and understood BMJ policy on declaration of interests and declare no competing interests.

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(6) Webb SM, Badia X, Barahona MJ, Colao A, Strasburger CJ, Tabarin A, et al. Evaluation of health-related quality of life in patients with Cushing's syndrome with a new questionnaire. Eur J Endocrinol 2008 May;158(5):623-30.

(7) Levy MJ, Matharu MS, Meeran K, Powell M, Goadsby PJ. The clinical characteristics of headache in patients with pituitary tumours. Brain 2005 Aug;128(Pt 8):1921-30.

(8) Crespo I, Esther GM, Santos A, Valassi E, Yolanda VG, De Juan-Delago M, Webb SM, Gómez-Ansón B, Resmini E. Impaired decision-making and selective cortical frontal thinning in Cushing's syndrome. Clin Endocrinol (Oxf). 2014 Dec;81(6):826-33. doi: 10.1111/cen.12564. Epub 2014 Sep 1. PubMed PMID: 25052342.

(9) Resmini E, Santos A, Gómez-Anson B, López-Mourelo O, Pires P, Vives-Gilabert Y, Crespo I, Portella MJ, de Juan-Delago M, Webb SM. Hippocampal dysfunction in cured Cushing's syndrome patients, detected by (1) H-MR-spectroscopy. Clin Endocrinol (Oxf). 2013 Nov;79(5):700-7. doi: 10.1111/cen.12224. Epub 2013 May 27. PubMed PMID: 23594250.

(10) Boscaro M, Sonino N, Scarda A, Barzon L, Fallo F, Sartori MT, et al. Anticoagulant prophylaxis markedly reduces thromboembolic complications in Cushing's syndrome. J Clin Endocrinol Metab 2002 Aug;87(8):3662-6.

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(14) Milian M, Honegger J, Teufel P, Wolf A, Psaras T. Tuebingen CD-25 is a sensitive tool to investigate health-related quality of life in Cushing's disease patients in the course of the disease. Neuroendocrinology 2013;98(3):188-99.

(15) Nelson LM, Forsythe A, McLeod L, Pulgar S, Maldonado M, Coles T, Zhang Y, Webb SM, Badia X. Psychometric evaluation of the Cushing's Quality-of-Life questionnaire. Patient. 2013;6(2):113-24. doi: 10.1007/s40271-013-0012-5. PubMed PMID: 23575965.

(16) Wagenmakers MA, Netea-Maier RT, Prins JB, Dekkers T, den HM, Hermus AR. Impaired quality of life in patients in long-term remission of Cushing's syndrome of both adrenal and pituitary origin: a remaining effect of long-standing hypercortisolism? Eur J Endocrinol 2012 Nov;167(5):687-95.

(17) Dimopoulou C, Athanasoulia AP, Hanisch E, Held S, Sprenger T, Toelle TR, Roemmler-Zehrer J, Schopohl J, Stalla GK, Sievers C. Clinical characteristics of pain in patients with pituitary adenomas. Eur J Endocrinol. 2014 Nov;171(5):581-91. doi: 10.1530/EJE-14-0375. Epub 2014 Aug 12. PubMed PMID: 25117460.

(18) Dimopoulou C, Ising M, Pfister H, Schopohl J, Stalla GK, Sievers C. Increased prevalence of anxiety-associated personality traits in patients with Cushing's disease: a cross-sectional study. Neuroendocrinology 2013;97(2):139-45.

(19) Trementino L, Ceccoli L, Concettoni C, Marcelli G, Michetti G, Boscaro M, Arnaldi G. Fracture risk assessment before and after resolution of endogenous hypercortisolism: Is the FRAX(®) algorithm useful? J Endocrinol Invest. 2014 Oct;37(10):957-65. doi: 10.1007/s40618-014-0126-1. Epub 2014 Jul 11. PubMed PMID: 25012159

(20) Scillitani A, Mazziotti G, Di Somma C, Moretti S, Stigliano A, Pivonello R, Giustina A, Colao A; ABC Group. Treatment of skeletal impairment in patients with endogenous hypercortisolism: when and how? Osteoporos Int. 2014 Feb;25(2):441-6. doi: 10.1007/s00198-013-2588-y. Epub 2013 Dec 6. PubMed PMID: 24311114.

(21) Arnaldi G, Mancini T, Tirabassi G, Trementino L, Boscaro M. Advances in the epidemiology, pathogenesis, and management of Cushing's syndrome complications. J Endocrinol Invest. 2012 Apr;35(4):434-48. Review. PubMed PMID: 22652826.

(22) Tóth M, Grossman A. Glucocorticoid-induced osteoporosis: lessons from Cushing's syndrome. Clin Endocrinol (Oxf). 2013 Jul;79(1):1-11. doi: 10.1111/cen.12189. Epub 2013 Apr 13. Review. PubMed PMID: 23452135.