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Cardiovascular and neuropsychiatric burden of hormonal excess syndromes

Kumulative Habilitationsschrift

Zur Erlangung der Lehrbefähigung

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List of abbreviations

ACTH: adrenocorticotropic hormone

ANCOVA: analysis of covariance

BDI: Beck Depression Inventory

BMI: body mass index

CD: Cushing's disease

EPQ-RK: Eysenck Personality Questionnaire

FBeK: Fragebogen zur Beurteilung des eigenen Körpers

FKB-20: Fragebogen zum Körperbild

FSH: follicle-stimulating hormone

GH: growth hormone

HDL: high-density lipoprotein

LDL: low-density lipoprotein

LH: luteinizing hormone

MIDAS: Migraine Disability Assessment

MRI: magnetic resonance imaging

NFPA: non-functioning pituitary adenomas

QoL: Quality of Life

TPQ: Cloninger Temperament and Personality Questionnaire

TSH: thyroid-stimulating hormone

TSS: transsphenoidal surgery

Introduction

Hormonal excess syndromes due to pituitary adenomas are rather rare, though various studies suggest that their prevalence might in some cases be 3.5 – 5 times higher than previously reported *(Daly et al., 2006).* Clinical presentation of pituitary adenomas is broad and can be divided into symptoms resulting from the change in endocrine status such as hormonal excess depending on the hormone produced or pituitary insufficiency and into symptoms resulting from the pituitary mass *per se*.

Patients with hormonal excess syndromes present with a variety of cardiovascular comorbidities depending on the hormone overproduced. Uncontrolled acromegaly is associated to increased morbidity and mortality, mainly due to cardiovascular comorbidities such as arterial hypertension, cardiomyopathy, heart valve disease, arrhythmias, atherosclerosis, coronary artery disease and cardiac dysfunction (*Colao et al. 2008; Fedrizzi et al. 2008*). These are supposed to be normalized or at least partially reversed after biochemical control is achieved (*Melmed 2009*). Cushing's disease (CD) is also associated to 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 *(Mancini et al., 2004; Pivonello et al., 2005; Boscaro et al., 2002)*. Transsphenoidal surgery (TSS) presents the treatment of choice for CD (*Biller et al., 2008*); remission rates following TSS are dependent on tumor size and extension, adenoma visibility on preoperative magnetic resonance imaging (MRI) as well as neurosurgical expertise and recurrence is frequent (*Tritos et al., 2011*). Treatment for hypercortisolism has been associated with a significant reduction in mortality and morbidity. However, even after long-term cure of the disease, patients exhibit a persistent unfavorable cardiometabolic

risk profile as in active hypercortisolemia *(Faggiano et al., 2003; Barahona et al., 2009).*

It is also increasingly recognized that patients with hormonal excesses suffer from neuropsychiatric side-effects, not only due to the neuroanatomic position of the pituitary mass itself. A few years ago, a high variability of emotional problems was detected in patients with different types of pituitary adenomas *(Flitsch et al. 2000).* Moreover, it is known that patients with pituitary adenomas frequently suffer from pain syndromes e.g. headache (*Levy et al. 2005; Kreitschmann-Andermahr et al. 2013*). Previous work from our group could show that acromegaly, a state of growth-hormone excess, is associated with an increased prevalence of affective disorders, anxiety-related personality traits, disturbances of the macroscopic brain tissue architecture and cognitive dysfunction *(Sievers et al. 2009; Sievers et al. 2012).*CD reflects chronic cortisol excess and also comprises a broad spectrum of psychiatric manifestations *(Pereira et al., 2012),* which do not necessarily correlate with the degree of hypercortisolism and often remain despite biochemical remission of the disease. Chronic exposure to elevated glucocorticoid levels has been suggested to lead to deficits in cognitive function and short-term memory as well as brain morphology changes *(Bourdeau et al., 2002; Forget et al., 2002)* and altered personality *(Sonino et al., 2006).* Impaired quality of life (QoL) in active CD is a consistent finding in many different studies having implications for the long-term management of the disease *(Lindsay et al. 2006; Feelders et al. 2012).*

Although the association between cardiovascular and neuropsychiatric comorbidities and pituitary disease is well established, to our knowledge only a few studies have investigated systematically and with standardised instruments cardiovascular and

especially neuropsychiatric aspects such as psychopathology, neuropsychology, personality, sleep, pain, brain architecture and quality of life in patients with hormonal excess syndromes and how these comorbidities and symptoms are affected by different therapy regimens.

Objectives

First aim of the work present herein was to investigate the clinical characteristics of pain in a large cohort of patients with pituitary disease, since clinical presentation of pituitary adenomas frequently involves pain due to structural and functional properties of the tumor. Growth hormone and IGF-1 play an important role in the regulation of metabolism and body composition. Subsequently, we went on to examine body composition and cardiovascular risk profile in a subgroup of patients with pituitary disease, patients with controlled acromegaly. In an attempt to investigate why diagnosis of acromegaly is delayed up to 10 years after disease onset despite obvious external/objective changes, we hypothesized that a lack of subjective perception of the disease state, possibly mediated by psychiatric or cognitive alterations, might contribute to the delayed initiation of a diagnostic work-up.

Patients with a different kind of pituitary adenoma, Cushing's disease, have been of particular interest within this project. In order to be able to look into long-term remission and recurrence rates of transsphenoidal surgery, the treatment of choice for CD, it was further necessary to conduct a retrospective analysis in a series incorporating different neurosurgeons in the Munich Metropolitan Region. In a parallel approach, we went on to investigate personality in patients with CD, since chronic hypercortisolism has been suggested to contribute to an altered personality profile in these patients.

Studies carried out and main findings

1. Pain in Patients with Pituitary adenomas

Dimopoulou C, Athanasoulia AP, Hanisch E, Held S, Sprenger T, Toelle TR, Roemmler-Zehrer J, Schopohl J, Stalla GK, Sievers C. The clinical characteristics of pain in patients with pituitary adenomas. Eur J Endocrinol. 2014 Aug 12. [Epub ahead of print]

Aim of this study was to describe the clinical characteristics of pain in patients with pituitary adenomas such as acromegaly, Cushing's disease (CD), prolactinomas and non-functioning pituitary adenomas (NFPA). We evaluated primary site of perceived pain, quality of pain, nociceptive vs neuropathic pain components, side shift, severity/intensity, frequency and duration, associated symptoms, trigger factors, family history in relation to pain as well as pain alleviating factors in patients with pituitary adenomas and how these might be influenced by modifiable factors such as tumor and treatment characteristics. The role of pain on disability and QoL was also assessed.

Patient demographics	All patients (n=278)		Acromegaly (n=81) (1)		CD (n=45) (2)		Prolactinoma (n=92) (3)		NFPA (n=60) (4)		Global test		*Post-hoc* tests (corrected for multiple comparisons, *P* values)					
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	χ^2	*P* value	1 vs 2	1 vs 3	1 vs 4	2 vs 3	2 vs 4	3 vs 4
Sex																		
Male	108	38.8	38	46.9	8	17.8	23	25	39	65	35.33	**0.000**	**0.004**	NS	NS	NS	**0.000**	**0.000**
Female	170	61.2	43	53.1	37	82.2	69	75	21	35								
											ANOVA							
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	*F*	*P*-value						
Age	52.8	13.2	55.5	11.8	46.2	11.1	49.2	13.8	60.2	10.6	15.68	**0.000**	**0.000**	NS	NS	NS	**0.000**	**0.000**
BMI	27.31	6.26	29.02	5.24	26.25	1.06	25.73	6.96	28.27	4.96	5.04	**0.002**	0.097	**0.003**	1.000	1.000	0.576	0.080
											Global test							
	N	%	*N*	%	*N*	%	*N*	%	*N*	%	χ^2	*P*-value						
Tumour characteristics																		
Macroadenoma	163	58.6	53	65	15	33.3	45	48.9	50	83	57.58	**0.000**	**0.000**	**0.000**	NS	NS	**0.000**	**0.000**
Microadenoma	87	31.3	6	7	30	66.7	47	51.1	4	7								
No data available	28	10.1	22	28	0	0	0	0	6	10								
Biochemical control	142	65.1	49	60.5	33	73.3	60	65.2	NA	NA	2.1	**0.350**						
Treatment																		
Surgery	182	65.5	73	90.1	44	97.8	13	14.8	52	86.7	177.85	**0.000**	NS	**0.000**	NS	**0.000**	NS	**0.000**
Radiotherapy	51	18.3	20	24.7	14	31.1	2	2.3	15	25.0	23.79	**0.000**	NS	**0.001**	NS	**0.001**	NS	**0.001**
Medical therapy	162	58.3	60	74.1	15	33.3	87	94.5	0	0.0	283.41	**0.000**	**0.000**	**0.000**	**0.000**	**0.000**	**0.000**	**0.000**
Comorbidities											χ^2	*P*-value						
Diabetes mellitus	43	15.5	22	27.2	11	24.4	4	4.7	6	10.0	18.32	**0.000**	NS	**0.000**	**0.028**	NS	NS	NS
Pituitary deficiency	147	52.9	48	59.3	32	71.1	22	24.4	45	75.0	66.1	**0.000**	NS	**0.000**	**0.004**	**0.000**	NS	**0.000**
Corticotrope	109	39.2	37	45.7	24	53.3	13	14.9	35	58.3	55.4	**0.000**	NS	**0.000**	**0.020**	**0.000**	NS	**0.000**
Thyreotrope	85	30.6	24	29.6	20	44.4	7	8.0	34	56.7	57.8	**0.000**	NS	**0.003**	**0.000**	**0.000**	NS	**0.000**
Gonadotrope	90	32.4	36	44.4	9	20.0	15	17.0	30	50.0	27.86	**0.000**	NS	**0.001**	NS	NS	**0.023**	**0.000**
Somatotrope	57	20.5	2	2.5	14	31.1	7	8.1	34	56.7	87.11	**0.000**	**0.000**	NS	**0.000**	**0.000**	**0.000**	**0.000**

CD, Cushing's disease; NFPA, non-functioning pituitary adenoma; NS, not significant; NA, not applicable.

Table 1: Demographic, tumor and treatment characteristics as well as comorbidities of the overall study population and according to each tumor subtype. *Adapted from Dimopoulou et al., 2014.*

The most common pain location for the whole group was the lower back (67%), followed by the neck (66%) and the shoulder/arm/hand region (66%). No pain side shift was reported by the majority of the pituitary adenoma patients (91%). The commonest quality of pain was described as "deep" (n=180; 65%). 62% of acromegaly, 80% of CD, 64% of prolactinoma and 58% of NFPA patients (p>0.05) reported "deep" pain. Pituitary adenoma patients reported on a scale of 0 (=no pain) to 10 (=most severe pain) a mean pain intensity of 4±2, the most severe pain intensity as 6±2 and the mildest pain intensity as 2±2within the last 4 weeks. CD patients reported the most severe pain intensity with 7±2, whereas prolactinoma patients reported the mildest pain intensity with 2±2. The majority of the study population (41%) complained of episodic pain, while 21% complained of permanent pain. CD patients were most frequently affected by permanent pain (31%). Chronic pain with pain attacks accounted only for 10% of patients. Median pain duration was 14±10 years.

	All patients		**Acromegaly** (1)		**CD** (2)		**Prolactinoma** (3)		**NFPA** (4)		**Global test**		***Post-hoc* tests** (corrected for multiple comparisons, *P*-values)					
	N	%	*N*	%	*N*	%	*N*	%	*N*	%	χ^2	*P*-value	1 vs 2	1 vs 3	1 vs 4	2 vs 3	2 vs 4	3 vs 4
Pain side shift																		
Yes	25	9.0	10	12.3	1	2.2	5	5.4	9	15	9.09	**0.028**	NS	NS	NS	NS	NS	NS
Primary pain site																		
Mouth/face/head	178	64.0	58	71.6	19	42.2	63	68.5	38	63.3	33.19	**0.016**	NS	NS	NS	NS	**0.020**	**0.037**
Neck/nape of the neck	184	66.2	57	70.4	21	46.7	64	69.6	42	70.0	37.25	**0.016**	**0.035**	NS	NS	NS	**0.011**	**0.033**
Shoulder/arm/hand	183	65.8	60	74.1	17	37.8	63	68.5	43	71.7	6.71	NS						
Abdominal area	174	62.6	60	74.1	18	40	53	57.6	43	71.7	39.21	**0.003**	**0.000**	NS	NS	**0.000**	**0.000**	NS
Lower back/bottom	186	66.9	59	72.8	21	46.7	63	68.5	43	71.7	30.79	**0.030**	NS	NS	NS	**0.016**	**0.004**	NS
Hip/leg/foot	182	65.5	60	74.1	17	37.8	62	67.4	43	71.7	24.03	**0.020**	NS	**0.020**	NS	**0.028**	NS	NS
Full body pain	178	64.0	58	71.6	15	33.3	63	68.5	42	70.0	27.08	**0.028**	**0.003**	NS	NS	**0.016**	**0.003**	NS
											ANCOVA[a]							
Pain intensity	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	*F*	*P*-value						
Mean	4.1	2.1	4.2	2.4	4.3	1.9	3.7	2.1	4.3	1.9	2.59	**0.014**	NS	NS	NS	NS	NS	NS
Most severe	6.1	2.4	5.8	2.4	6.7	2.1	6.1	2.6	5.8	2.3	1.14	NS						
Mildest	1.8	1.8	2.0	2.0	2.1	2.1	1.5	1.7	1.8	1.5	3.24	**0.003**	NS	NS	NS	NS	NS	NS
											Global test							
Pain quality	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	χ^2	*P*-value						
Deep pain	180	64.7	50	61.7	36	80.0	59	64.1	35	58.3	1.31	NS						
Surface pain	23	8.3	7	8.6	3	6.7	11	12.0	2	3.3	3.96	NS						
Pain outside the body	1	0.4	0	0	0	0	1	1.1	0	0	2.07	NS						
Pain frequency																		
Episodic	115	41.4	28	34.6	22	48.9	41	41.6	24	40.0	3.86	NS						
Permanent/chronic	58	20.9	20	24.7	12	30.8	14	15.2	12	20.0								
Chronic with pain attacks	28	10.1	9	11.1	5	12.8	10	10.9	4	6.7								

CD, Cushing's disease; NFPA, non-functioning pituitary adenoma; ANCOVA, analysis of covariance; NS, not significant.
[a]Corrected for age, sex, BMI and tumor type.

Table 2: Pain side shift, quality, intensity and frequency amongst tumor subtypes. *Adapted from Dimopoulou et al., 2014.*

Visual disturbances (28%), noise sensitivity (19%), nausea (19%) and photophobia (18%) were the commonest pain associated symptoms. Pain was accompanied by visual disturbances in 25%, 27% and 28% of the acromegaly, prolactinoma and NFPA patients, respectively, whereas CD patients most frequently associated pain to photophobia (29%). Pain appeared to be triggered in 41% of the pituitary adenoma patients by physical stress, followed by emotional stress (21%) and other causes (16%).

"Resting" (44%) and the use of motion/exercise (25%) comprised non-pharmacological alleviating factors. No family history of pain was recorded in the majority of the pituitary adenoma patients (86%) (acromegaly 83%; CD 84%; prolactinoma 84%, NFPA 93%) (p>0.05).

	All patients		**Acromegaly** (1)		**CD** (2)		**Prolactinoma** (3)		**NFPA** (4)		**Global test**		***Post-hoc* tests** (corrected for multiple comparisons, *P*-values)					
	N	%	*N*	%	*N*	%	*N*	%	*N*	%	χ^2	*P*-value	1 vs 2	1 vs 3	1 vs 4	2 vs 3	2 vs 4	3 vs 4
Associated features																		
Nausea	52	18.7	14	17.2	11	24.4	10	10.9	7	11.7	21.44	**0.011**	NS	NS	NS	NS	NS	NS
Vomiting	21	7.6	7	8.6	5	11.1	7	7.6	2	3.3	14.99	NS						
Photophobia	50	18.0	9	11.1	13	28.9	20	21.7	8	13.3	14.98	NS						
Noise sensitivity	53	19.0	12	14.8	17	37.8	17	18.5	7	11.7	21.23	**0.012**	NS	NS	NS	NS	NS	NS
Visual disturbances	77	27.7	20	24.7	15	33.3	25	27.2	17	28.3	33.03	**0.000**	NS	NS	NS	NS	NS	NS
Oedema/Erythema	43	15.5	13	16.0	11	24.5	10	10.9	9	15.0	28.88	**0.001**	NS	NS	NS	NS	NS	NS
Hypersensitivity of the skin	30	10.8	12	14.8	11	24.5	15	16.3	11	18.4	27.42	**0.001**	NS	NS	NS	NS	NS	NS
Triggers/causes																		
Disease	79	28.4	27	33.3	25	55.6	15	16.3	12	20.0	20.71	**0.000**	NS	**0.044**	NS	**0.000**	**0.003**	NS
Surgery	44	15.8	14	17.3	12	26.7	8	8.7	10	16.7	5.52	NS						
Physical stress	114	41.0	30	37.0	25	55.6	36	39.1	23	38.3	4.23	NS						
Emotional stress	57	20.5	14	17.3	13	28.9	25	27.2	5	8.3	1.76	NS						
Other cause	45	16.2	12	14.8	10	22.2	13	14.1	10	16.7	10.39	**0.015**	NS	NS	NS	NS	NS	**0.013**
No cause	23	8.3	6	7.4	1	2.2	8	8.7	8	13.3	3.44	NS						
Accident	13	4.7	5	6.2	0	0	6	6.5	2	3.3	0.55	NS						
Hereditary	14	5.0	5	6.2	1	2.2	3	3.3	5	8.3	5.83	NS						
Alleviating factors																		
Non-pharmacologic																		
Physical stress	5	1.8	1	1.2	1	2.2	3	3.3	0	0.0	5.22	NS						
One-sided posture	7	2.5	4	4.9	1	2.2	2	2.2	0	0.0	8.13	NS						
Motion/exercise	70	25.2	25	30.9	17	37.8	17	18.5	11	18.3	7.76	NS						
Rest	122	43.9	40	49.4	26	57.8	37	40.2	19	31.7	17.08	NS						
Family history																		
Positive	40	14.4	14	17.3	7	15.6	15	16.3	4	6.7	3.43	NS						

CD, Cushing's disease; NFPA, non-functioning pituitary adenoma; NS, not significant.

Table 3: Pain associated features, trigger factors, alleviating factors and family history within the study population. *Adapted from Dimopoulou et al., 2014.*

The majority of the patients (72%) suffered from little or no headache-related disability (Grade I) on daily life, according to MIDAS. 73% of the acromegalic, 63% of the CD, 72% of the prolactinoma and 70% of the NFPA subjects had little or no headache-related disability within the subgroups. 25% of the CD population reported severe headache-related disability (Grade IV) though.

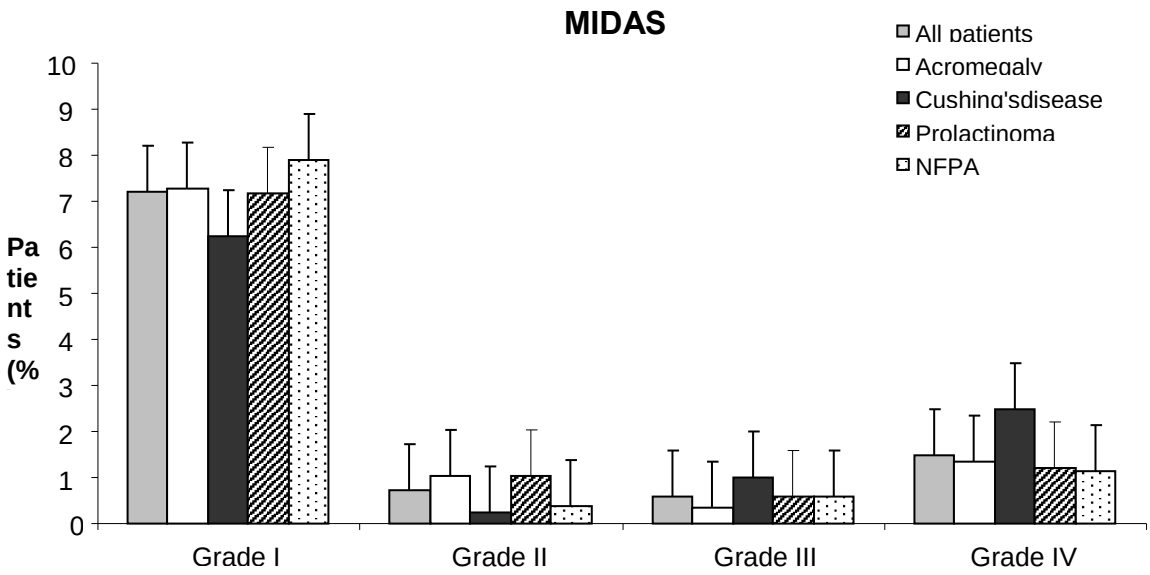


Figure 1: Distribution of Migraine Disability Assessment (MIDAS) scores amongst tumor types and for the group as whole. *Adapted from Dimopoulou et al., 2014.*

The highest MIDAS scores were recorded in the CD and NFPA patient group (20±40 and 12±38, respectively). The mean MIDAS score for the whole group was 12±33 days.

Screening criteria for a nociceptive pain component were fulfilled in the majority of the patients (80%), followed by uncertain pain (11%) and a neuropathic pain component (1%). 84% of the acromegalic, 78% of the CD, 72% of the prolactinoma and 88% of the NFPA subjects complained of nociceptive pain within the subgroups(figure 2).

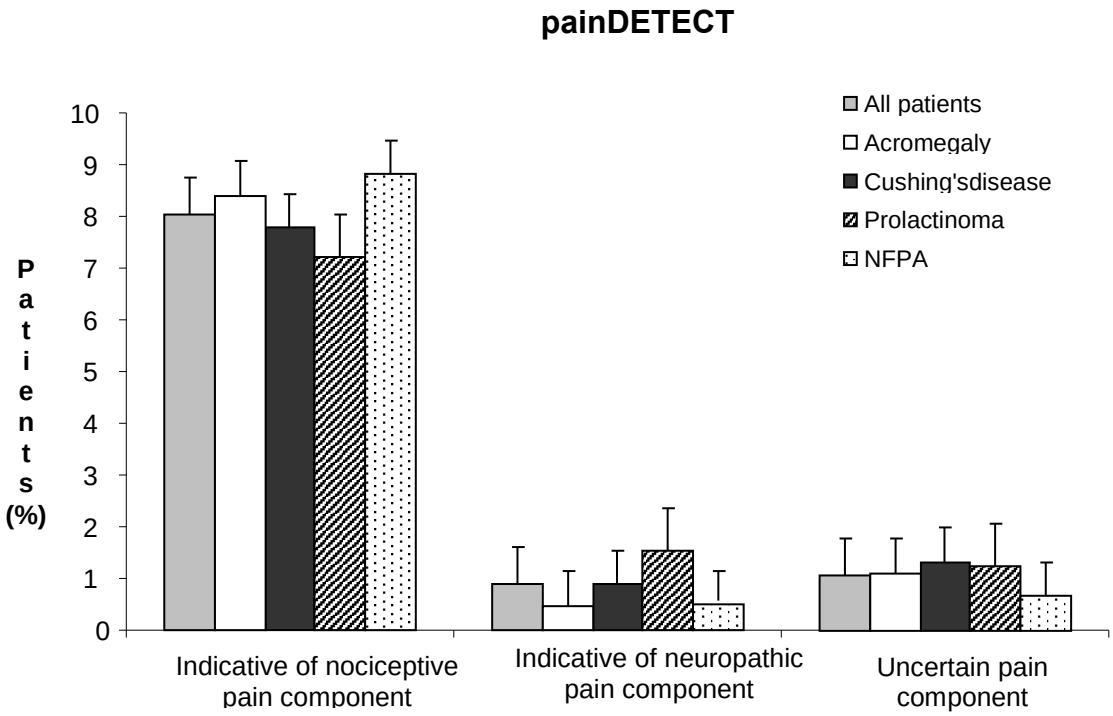


Figure 2: Distribution of painDETECT scores amongst tumor and for the group as whole. *Adapted from Dimopoulou et al., 2014.*

The highest mean painDETECT scores were seen in the prolactinoma and CD patient group (9±8 and 8±7, respectively). Mean painDETECT score for the whole group was 7±7.

There was significant difference regarding the pain DETECT score (p=0.007) between patients with hormonal hypersecretion independent of tumor type and patients with biochemically controlled pituitary disease. Modifiable factors such as tumor size, genetic predisposition, previous surgery, irradiation or medical therapy did not show significant impact on headache-related disability (MIDAS score) or neuropathic pain components (painDETECT score).

	BDI		EQ-VAS	
	r	*P*-value	*r*	*P*-value
painDETECT				
Total	0.431	**0.000**	−0.415	**0.000**
Acromegaly	0.318	**0.011**	−0.342	**0.007**
Cushing's disease	0.719	**0.000**	−0.577	**0.000**
Prolactinoma	0.528	**0.000**	−0.479	**0.000**
NFPA	0.327	**0.011**	−0.283	**0.031**
MIDAS				
Total	0.290	**0.009**	−0.412	**0.000**
Acromegaly	0.109	NS	−0.451	**0.000**
Cushing's disease	0.420	**0.007**	−0.347	**0.030**
Prolactinoma	0.126	NS	−0.265	**0.036**
NFPA	0.460	**0.001**	−0.216	NS

BDI, Beck Depression Inventory; EQ-VAS, EQ visual analogue scale of the EuroQOL questionnaire; MIDAS, migraine disability assessment; *r*, Pearson's correlation coefficient; NFPA, non-functioning pituitary adenoma; NS, not significant.

Table 4: Pearson's *r* correlation coefficients between neuropathic pain components (painDETECT) and headache-related disability (MIDAS) with depression (BDI) and health-related quality of life (visual analogue scale EQ-VAS) in all 278 patients and within the subgroups. . *Adapted from Dimopoulou et al., 2014.*

All correlations between neuropathic pain, depression and impaired health-related quality of life showed statistical significance in ($p<0.05$). As far as headache-related disability was concerned, there was again statistical significance in nearly all correlations with depression except for acromegalic ($p=0.412$) and prolactinoma patients ($p=0.315$), as well as with health-related quality of life except for NFPA patients ($p=0.127$).

Taken together, these data demonstrate that: (i) bodily pain is highly prevalent in patients with pituitary adenomas independent of the tumor type; (ii) compared to other patient groups, CD patients are especially susceptible to pain; iii) most pituitary patients suffer from nociceptive pain; (iv) a high incidence of headache was recorded

independent of tumor type; however, the majority of the study population reported little or no headache-related disability in everyday life; (v) modifiable factors such as tumor size, genetic predisposition, previous surgery, irradiation or medical therapy do not seem to have a significant impact on pain; (vi) there is significant correlation between pain and pain-related disability with depression and impaired QoL.

2. Cardiovascular risk profile in Patients with Acromegaly

Dimopoulou C*, Sievers C*, Wittchen HU, Pieper L, Klotsche J, Roemmler J, Schopohl J, Schneider HJ, Stalla GK. * both authors contributed equally. Adverse anthropometric risk profile in biochemically controlled acromegalic patients: comparison with an age- and gender-matched primary care population. Pituitary. 2010 Feb 4. [Epub ahead of print]

Aim of this study was to evaluate the cardiovascular risk profile of "biochemically controlled" acromegalic patients by comparing their anthropometric parameters and cardiovascular risk biomarkers to an age- and gender-matched primary care control group. We performed stratified analyses in diabetic and non-diabetic patients separately, since acromegaly is associated with an increased risk of diabetes mellitus, which might influence the calculations.

Anthropometric parameters, such as weight, BMI, waist and hip circumference (86.6±17.8 vs. 79.8±17.4 kg; p=0.002; 29.2±5.2 vs. 27.5±5.6 kg/m^2; p=0.014; 100.0±14.3 vs. 95.7±15.5 cm; p=0.026; 110.6±9.2 vs. 105.6±12.0 cm; p=0.001, respectively) were significantly higher in the whole group of acromegalic patients in comparison to their respective controls. Cardiovascular risk biomarkers such as fasting plasma glucose, total cholesterol, triglycerides and HDL levels were more favorable in the acromegalic group compared to the age- and gender-matched controls, interestingly. As far as comorbidities were concerned, acromegalic patients suffered significantly more often from hypertension (54.3 vs. 37.8 %; p=0.008) and malignancies (11.1 vs. 3.1 %; p=0.005), but less often from myocardial infarction (1.2 vs. 36.7%; p=0.001), compared to their controls.

	Patients with acromegaly (n = 81)		DETECT-control group (n = 320)		P-value
	n	%	n	%	
Comorbidities					
Hypertension	44	54.3	121	37.8	**0.008**
Diabetes mellitus	22	27.2	58	18.1	0.073
Coronary heart disease	7	8.6	30	9.4	0.840
Myocardial infarction	1	1.2	11	36.7	**0.001**
Cerebral insult	4	4.9	0	0.0	–
Malignancies	9	11.1	10	3.1	**0.005**
Pituitary deficiency	48	59.3			
Corticotrope deficiency	35	43.2			
Thyreotrope deficiency	22	27.2			
Gonadotrope deficiency	33	40.7			
Growth hormone deficiency	3	3.7			
		Mean (SD)		Mean (SD)	P-value
Anthropometric parameters					
Height (cm)		172.4 (12.0)		170.1 (9.3)	0.107
Weight (kg)		86.6 (17.8)		79.8 (17.4)	**0.002**
BMI (kg/m^2)		29.2 (5.2)		27.5 (5.6)	**0.014**
Waist circumference (cm)		100.0 (14.3)		95.7 (15.5)	**0.026**
Hip circumference (cm)		110.6 (9.2)		105.6 (12.0)	**0.001**
Waist to height ratio		0.58 (0.09)		0.56 (0.09)	0.174
Biochemical parameters					
IGF-1 (µg/L)		214.2 (161.2)		131.5 (54.3)	**0.000**
Cardiovascular risk biomarkers					
Fasting plasma glucose (mg/dL)		93.5 (16.5)		104.1 (35.1)	**0.001**
HbA1c (%)		5.7 (0.5)		5.6 (1.0)	0.550
Total cholesterol (mg/dL)		215.8 (39.5)		226.6 (44.0)	**0.045**
Triglycerides (mg/dL)		121.1 (63.6)		160.8 (155.3)	**0.001**
HDL (mg/dL)		60.4 (21.4)		53.0 (17.6)	**0.009**
LDL (mg/dL)		139.4 (37.4)		131.0 (32.4)	0.093
Lipoprotein (a) (mg/dL)		36.1 (43.5)		33.3 (47.3)	0.707

Note: Significant effects are bold typed

Table 5: Comparisons of comorbidities, anthropometric parameters and cardiovascular risk biomarkers between patients with acromegaly (n=81) and the age- and gender-matched DETECT-controls (n=320). *Adapted from Dimopoulou et al., 2010.*

The study group was further stratified into controlled and uncontrolled patients and compared to their respective primary care control patients.

Anthropometric measurements such as weight (85,6±17.9 vs. 78.5±18.5 kg; p=0.015), BMI (29.5±5.9 vs. 27.3±5.8 kg/m^2; p=0.020), waist (100.9±16.8 vs. 94.8±15.5 cm; p=0.031) and hip circumference (110.7±9.9 vs. 105.0±11.7 cm; p=0.001) were significantly higher in biochemically controlled patients in comparison to their respective DETECT controls. On the other hand, cardiovascular risk biomarkers, such as fasting plasma glucose (90.9±16.7 vs. 104.8±39.3 mg/dL; p=0.000) and triglycerides

(118.5±59.4 vs.153.8±123.1 mg/dL; p=0.006), were significantly lower in biochemically controlled patients. We performed the same analyses excluding patients who had been irradiated or were pituitary-deficient, since radiation might be also involved in the genesis of pituitary deficiency with effects on both body composition and cardiovascular risk biomarkers. Similar results with significant differences in BMI, waist and hip circumference between the groups (p=0,039, 0,015 and 0,001, respectively) were observed (table 6).

	Patients with uncontrolled acromegaly (n = 31)		Patients with controlled acromegaly (n = 49)		P-value controlled versus uncontrolled acromegaly	DETECT-control group, patients with uncontrolled acromegaly (n = 120)		P-value versus uncontrolled acromegaly	DETECT-control group, patients with controlled acromegaly (n = 196)		P-value versus controlled acromegaly
	n	%	n	%		n	%		n	%	
Comorbidities											
Hypertension	16	51.6	27	55.1	0.762	46	38.3	0.191	75	38.3	0.037
Diabetes mellitus	7	22.6	15	30.6	0.438	23	19.2	0.676	35	17.9	**0.049**
Coronary heart disease	4	12.9	3	6.1	0.309	11	9.2	0.544	19	9.7	0.443
Myocardial infarction	0	0.0	1	2.0	–	4	36.4	–	7	36.8	**0.001**
Cerebral insult	0	0.0	4	8.2	–	0	0.0	–	0	0.0	–
Malignancies	5	16.1	4	8.2	0.283	5	4.2	**0.029**	5	2.6	0.080
			Mean (SD)		Mean (SD)			Mean (SD)			Mean (SD)
Anthropometric parameters											
Height (cm)			174.5 (13.5)		170.7 (10.6)	0.188		170.9 (9.9)	0.165		169.3 (8.7)	0.391
Weight (kg)			87.1 (17.2)		85.6 (17.9)	0.707		81.4 (15.4)	0.101		78.5 (18.5)	**0.015**
BMI (kg/m^2)			28.5 (4.0)		29.5 (5.9)	0.376		27.9 (5.2)	0.523		27.3 (5.8)	**0.020**
Waist circumference (cm)			98.2 (9.8)		100.9 (16.8)	0.384		97.0 (15.6)	0.606		94.8 (15.5)	**0.031**
Hip circumference (cm)			109.9 (7.4)		110.7 (9.9)	0.719		106.5 (12.6)	0.063		105.0 (11.7)	**0.001**
Waist to height ratio			0.56 (0.06)		0.59 (0.10)	0.190		0.57 (0.09)	0.712		0.56 (0.09)	0.089
Biochemical parameters											
IGF-1 (μg/L)			317.1 (216.7)		149.1 (47.7)	**0.000**		135.5 (52.5)	**0.000**		128.7 (55.5)	**0.011**
Cardiovascular risk biomarkers											
Fasting plasma glucose (mg/dL)			97.5 (15.9)		90.9 (16.7)	0.084		103.7 (27.3)	0.107		104.8 (39.3)	**0.000**
HbA1c (%)			5.8 (0.5)		5.6 (0.4)	0.104		5.6 (0.9)	0.069		5.7 (1.1)	0.566
Total cholesterol (mg/dL)			204.6 (42.1)		223.6 (36.8)	0.058		225.0 (38.3)	**0.022**		227.7 (47.6)	0.534
Triglycerides (mg/dL)			118.2 (62.3)		118.5 (59.4)	0.987		174.4 (198.5)	**0.011**		153.8 (123.1)	**0.006**
HDL (mg/dL)			62.2 (24.8)		60.0 (19.2)	0.702		51.2 (17.5)	**0.040**		54.1 (17.6)	0.077
LDL (mg/dL)			128.8 (40.1)		146.9 (34.2)	0.070		129.6 (28.5)	0.929		131.9 (34.8)	**0.013**
Lipoprotein (a) (mg/dL)			40.3 (48.6)		34.1 (41.7)	0.706		32.3 (43.4)	0.585		34.0 (49.9)	0.985

Note: Significant effects are bold typed

Table 6: Comparisons of comorbidities, anthropometric parameters and cardiovascular risk biomarkers between biochemically controlled (n=49) and uncontrolled patients (n=31) and the age- and gender-matched DETECT-controls (n=196 and n=120, respectively). *Adapted from Dimopoulou et al., 2010.*

We carried out further stratified analyses with acromegalic patients and primary care controls with and without type 2 diabetes mellitus, in order to exclude type 2 diabetes mellitus as a potential confounder for our calculations. Twenty-two acromegalic subjects were diagnosed with diabetes mellitus (age- and gender-matched control group of patients with diabetes mellitus n=88) during the course of the disease or treatment.

	Patients with acromegaly and no diabetes mellitus + (n = 59)		Patients with acromegaly and diabetes mellitus (n = 22)		P-value no diabetes versus diabetes	DETECT-control group, patients with no diabetes (n = 232)		P-value versus no diabetes	DETECT-control group, patients with diabetes (n = 88)		P-value versus diabetes
	n	%	n	%		n	%		n	%	
Comorbidities											
Hypertension	29	49.2	15	68.2	0.133	88	37.9	**0.007**	33	37.5	0.715
Diabetes mellitus	–	–	–	–		42	18.1	–	16	18.2	–
Coronary heart disease	5	8.5	2	9.1	0.930	24	10.3	0.437	6	6.8	0.130
Myocardial infarction	1	1.7	0	0.0	–	7	29.2	**0.002**	4	66.7	–
Cerebral insult	1	1.7	3	13.6	0.063	0	0.0	–	0	0.0	–
Malignancies	6	10.2	3	13.6	0.662	7	3.0	**0.015**	3	3.4	0.227
		Mean (SD)		Mean (SD)			Mean (SD)			Mean (SD)	
Anthropometric parameters											
Height (cm)		174.7 (12.1)		166.0 (9.1)	**0.001**		171.1 (9.2)	**0.006**		167.3 (9.0)	0.060
Weight (kg)		87.3 (17.7)		84.6 (18.6)	0.559		80.5 (17.1)	**0.000**		77.7 (18.2)	0.449
BMI (kg/m^2)		28.6 (4.8)		30.7 (6.2)	0.155		27.5 (5.3)	**0.015**		27.6 (6.1)	0.831
Waist circumference (cm)		98.9 (10.9)		102.8 (21.4)	0.449		96.3 (15.9)	**0.003**		93.8 (14.3)	0.596
Hip circumference (cm)		110.8 (8.7)		110.2 (10.7)	0.830		105.6 (12.1)	**0.000**		105.6 (11.9)	0.829
Waist to height ratio		0.57 (0.06)		0.61 (0.13)	0.131		0.56 (0.09)	0.127		0.56 (0.08)	0.870
Biochemical parameters											
IGF-1 (µg/L)		218.6 (152.6)		202.7 (185.5)	0.720		135.4 (56.2)	**0.000**		121.4 (48.0)	0.057
Cardiovascular risk biomarkers											
Fasting plasma glucose (mg/dL)		89.9 (11.9)		103.6 (22.8)	**0.010**		104.3 (36.8)	**0.011**		103.5 (30.2)	**0.000**
HbA1c (%)		5.6 (0.4)		5.9 (0.6)	**0.038**		5.6 (1.0)	**0.000**		5.7 (0.9)	**0.000**
Total cholesterol (mg/dL)		214.3 (39.0)		219.8 (41.7)	0.616		227.1 (45.9)	**0.031**		225.3 (38.9)	0.787
Triglycerides (mg/dL)		107.1 (54.4)		157.3 (72.5)	**0.007**		158.8 (128.2)	**0.000**		166.2 (211.8)	0.071
HDL (mg/dL)		59.9 (21.8)		61.7 (20.8)	0.748		52.9 (18.0)	0.095		53.3 (16.5)	**0.010**
LDL (mg/dL)		139.7 (37.0)		138.7 (39.4)	0.920		131.4 (33.5)	0.195		130.2 (29.4)	0.209
Lipoprotein (a) (mg/dL)		45.6 (48.8)		13.8 (8.5)	**0.003**		31.6 (44.3)	0.282		37.6 (54.7)	**0.021**

Note: Significant effects are bold typed

Table 7: Comparisons of comorbidities, anthropometric parameters and cardiovascular risk biomarkers between acromegalic patients with (n=22) and without diabetes mellitus (n=59) and the age- and gender-matched DETECT-controls (n=88 and n=232, respectively). *Adapted from Dimopoulou et al., 2010.*

We did not detect any significant differences in anthropometric parameters between acromegalic patients with diabetes mellitus and controls with diabetes mellitus, as presented in table 7. Acromegalic patients with diabetes mellitus even showed an

improved cardiovascular risk profile regarding HDL (61.7±20.8 vs. 53.3±16.5 mg/dL; p=0.010) and lipoprotein (a) levels (13.8±8.5 vs. 37.6±54.7 mg/dL; p=0.021), but not regarding total cholesterol, triglycerides and LDL. Acromegalic patients without diabetes mellitus had significantly more often hypertension (49.2 vs. 37.9%; p=0.007), but lower fasting plasma glucose (89.9±11.9 vs. 104.3±36.8 mg/dL; p=0.011), total cholesterol (214.3 ±39.0 vs. 227.1 ±45.9 mg/dL; p=0.031) and triglycerides' levels (107.1 ±54.4 vs. 158.8 ±128.2 mg/dL; p=0.000), compared to their respective controls.

Taken together, this study demonstrates that biochemically controlled acromegalic patients exhibit an adverse anthropometric risk profile compared to an age- and gender-matched primary care control cohort.

3. Body image in Patients with Acromegaly

Dimopoulou C, Leistner SM, Ising M, Schneider HJ, Schopohl J, Rutz S, Kosilek R, Frohner R, Stalla GK, Sievers C. Body Image Perception in Acromegaly is Not Associated with Objective Acromegalic Changes, But Depends on Depressive Symptoms. Neuroendocrinology. 2016 Jul 25. [Epub ahead of print]

Aim of this study was to investigate whether acromegalic patients show altered body image perception compared to a clinical control group of patients with non-functioning pituitary adenomas (NFPA) who lack any physical/bodily changes. The underlying hypothesis was that acromegalic patients might only show mildly altered body image perception despite marked objective changes. Delayed disease diagnosis might be due to this inability to recognize objective physical changes. Additionally, we analyzed associations for impaired body image with other potentially causal factors e.g. objective acromegalic changes as judged by medical experts, psychiatric pathology such as depression and cognitive impairment, time of hormonal excess and treatment status.

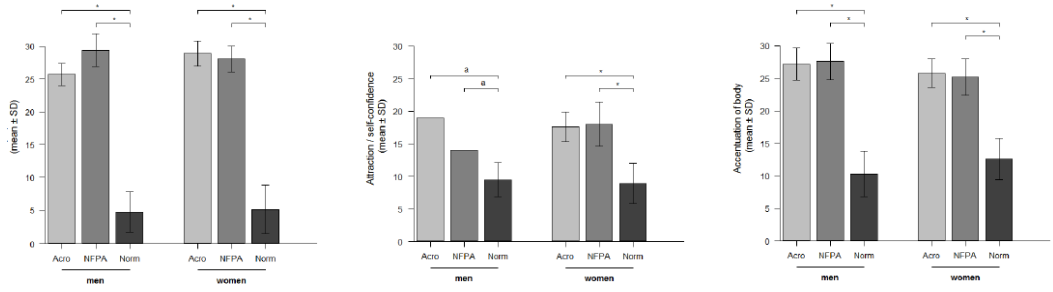
Acromegalic men had significantly higher mean values in the negative body image scale (22.5±6.3 vs. 18±4.6; $p< 0.001$), whereas both acromegalic men and women scored significantly lower in the vital body dynamics scale (31.3±7.9 vs. 38±4.2; $p< 0.001$ for men and 27.4±7.8 vs. 37 ±5.8; $p< 0.001$ for women) of the FKB-20 questionnaire, compared to normative values.

	Groups		Effect	
	acromegaly (n = 81)	NFPA (n = 60)	test statistic	p value
Sex, male/female	38/43 (46.9/53.1)	39/21 (65.0/35.0)	$\chi^2 = 4.549$	0.033
Age, years	55.69±12.17	60.22±10.61	t = 2.304	0.023
Body mass index	29.04±5.20	28.49±5.10	–	n.s.
Primary adenoma type				
Micro	8.7	6.7	–	n.s.
Macro	66.5	81.7	–	n.s.
Unknown size	24.8	11.6	–	n.s.
Treatment				
Surgery	91.4	86.7	–	n.s.
Radiotherapy	24.7	25.0	–	n.s.
Satisfactory treatment status[a]	60.5	–	–	–
Comorbidities				
Arrhythmia	19.8	5.0	$\chi^2 = 5.572$	0.022
Cardiomyopathy	11.1	0	$\chi^2 = 6.775$	0.011
Cerebrovascular disease	4.9	5.0	–	n.s.
Arterial hypertension	54.3	45.0	–	n.s.
Coronary heart disease	8.6	3.3	–	n.s.
Myocardial infarction	1.2	1.7	–	n.s.
Arthralgia	66.7	41.7	$\chi^2 = 6.578$	0.014
Arthropathy	32.1	15.0	–	n.s.
Carpal tunnel syndrome	46.9	18.3	$\chi^2 = 10.295$	0.002
Diabetes mellitus	27.2	10.0	$\chi^2 = 5.897$	0.018
Pathological glucose intolerance	28.4	0	$\chi^2 = 17.785$	<0.001
Pituitary insufficiency	61.7	75.0	$\chi^2 = 10.900$	0.001
Corticotrope	45.7	58.3	$\chi^2 = 55.400$	0.020
Thyreotrope	29.6	56.7	$\chi^2 = 57.800$	0.000
Gonadotrope	44.4	50.0	$\chi^2 = 27.860$	n.s.
Somatotrope	2.5	56.7	$\chi^2 = 87.110$	0.000
Sleep apnea	34.6	10.0	$\chi^2 = 10.097$	0.002
Cancer	11.1	10.0	–	n.s.
Pulmonary disease	6.2	1.7	–	n.s.
BDI-II[†]	9.00±8.47	7.93±7.20	–	n.s.

Data represented as n (%), mean ± standard deviation or percentage. n.s. = Groups do not differ significantly with $\alpha < 0.05$. [a] According to laboratory values. [†] Higher values equal higher depression score.

Table 8: Clinical characteristics of the study population. *Adapted from Dimopoulou et al., 2016.*

Further, acromegalic patients (both men and women) suffered from an unfavorable body image, showing significantly higher mean values in 2 of the 3 FBeK scales ($p< 0.001$ for insecurity/paresthesia and $p< 0.001$ for accentuation of the body) compared to normative values. It was of interest that acromegalic women scored significantly higher in the attraction/self-confidence scale (17.6 ±2.3 vs. 9 ±3.1; $p< 0.001$).



SD: standard deviation, Acro = Acromegaly, NFPA = Non-functioning pituitary adenomas, Norm = Norm values of students
* = Groups differ significantly with p < 0.05
* = Groups are too small to analyse differences because of missing data

Figure 3: Comparisons between patients with acromegaly, patients with NFPA and norm values of students in FBeK-scales. *Adapted from Dimopoulou et al., 2016.*

There was significant difference between acromegalic and NFPA patients only in the vital body dynamics scale of the FKB-20 questionnaire (F = 5.040, p = 0.003), whereby NFPA women showed the lowest (24.8±6.3) and NFPA men the highest scores (31.6±6.7). There were no significant differences between acromegalic and NFPA patients (both groups divided into men and women) in any of the three FbeK subscales.

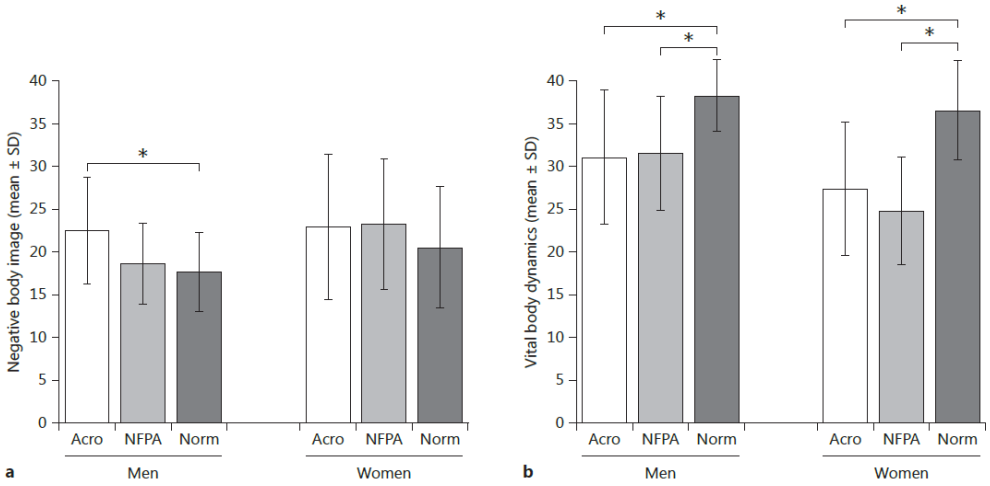


Figure 4: Comparisons between patients with acromegaly, patients with NFPA and norm values of students in FKB-20-scales. *Adapted from Dimopoulou et al., 2016.*

Further, we associated impaired body image in acromegalic patients with other potentially causal factors. Regarding the FKB-20, we tested differences in body image for patients without depression (BDI < 10), patients with mild or moderate depression (10≤ BDI < 18) and patients with clinical depression as indicated by BDI equal or larger than 18. As expected, patients with clinical depression (BDI ≥ 18) scored significantly lower in vital body dynamics ($F = 29.967$, $p < 0.001$) and significantly higher in negative body image ($F = 20.293$, $p < 0.001$), according to the FKB-20 (figure 5).

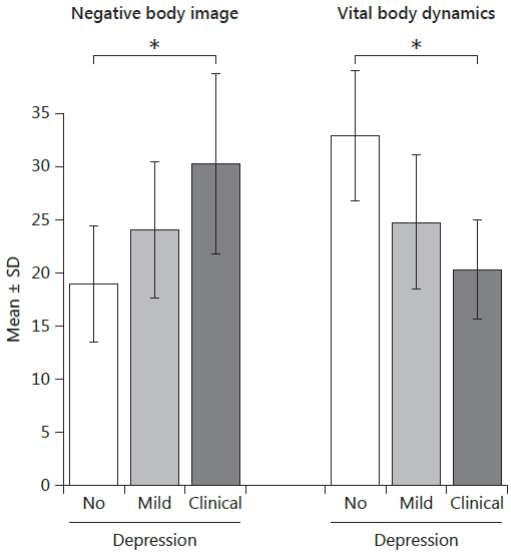


Figure 5: Differences between patients without depression, with mild or moderate depression and with clinical depression in FKB-20-scales. *Adapted from Dimopoulou et al., 2016.*

We went on to test whether cognitive decline might be responsible for disturbed body image and analyzed differences in body image perception between acromegalic patients with cognitive impairment – defined as a percentile ranking of lower than 16 – and those with normal cognitive status; we did not detect any significant differences between the two groups.

In a subgroup of acromegalic patients with available frontal and side photographs of the faces (n=39), patients were grouped into subjects with mild (n=14), moderate (n=19), and severe acromegaly (n=6) by expert opinion and we tested whether different

degrees of severity might lead to different body image. No significant correlations between visual disease severity and unfavorable body image were found (table 9).

Severity	Acromegaly (n = 81)			Effect[a]	
	mild (n = 14)	moderate (n = 19)	severe (n = 6)	test statistic	p value
FBeK scales					
Insecurity/paresthesia[↓]	28.40±0.55	29.43±2.76	30.00±1.00	F = 0.732	0.503
Attraction/self-confidence[↓]	19.00±1.00	17.40±2.41	–[b]	F = 0.075	0.795
Accentuation of body[↓]	27.25±1.26	26.44±2.79	27.00±1.63	F = 0.217	0.808
FKB-20 scales					
Negative body image[↓]	20.36±8.24	22.24±8.72	20.60±6.50	F = 0.191	0.827
Vital body dynamics[↑]	29.20±7.84	30.80±7.78	37.00±4.30	F = 1.563	0.229

Data represented as mean ± standard deviation. [↑] Higher values equal better body image. [↓] Lower values equal better body image. [a] All differences are controlled for differences in ages between severity groups (ANCOVA). [b] Groups are too small to analyse differences because of missing data.

Table 9: Disease severity and body image perception. *Adapted from Dimopoulou et al., 2016.*

Further analysis associating disturbed body image with modifiable factors such as time of hormonal excess or satisfactory treatment status according to laboratory values did not detect any significant correlations with any scale of the body image questionnaires.

Taken together, this study demonstrates that body image perception in patients with acromegaly does not differ from patients with NFPA, although these patients do not exhibit physical/bodily changes. This lack of bodily self-perception correlates to the presence of depression, though was not different between patients with different disease severity, different duration of hormonal excess or biochemical control of the disease.

4. Outcomes of Transsphenoidal surgery for Cushing's disease

Dimopoulou C, Schopohl J, Rachinger W, Buchfelder M, Honegger J, Reincke M, Stalla GK. Long-term remission and recurrence rates after first and second transsphenoidal surgery for Cushing's disease: Care reality in the Munich Metropolitan Region. Eur J Endocrinol. 2013 Nov 11. [Epub ahead of print]

Aim of our study was to assess in the long-term remission and recurrence rates of CD after 1st and after 2ndtranssphenoidal surgery (TSS) in the Munich Metropolitan Region, which is accommodated by three major tertiary university neurosurgical centers and multiple, smaller neurosurgical centers, reflecting care reality in this region. Our hypothesis was that remission rates might be lower and recurrence rates might be higher in our series comprising different neurosurgeons, when compared to remission and recurrence rates published from single-surgeon expert neurosurgical series. Additionally, we focused on the role of 2nd TSS in the current therapeutic regimen for CD, correlated postoperative hypocortisolism and risk of recurrence and described our therapeutic strategy in patients with persistent disease after TSS.

	First TSS ($n=120$)	**Second TSS** ($n=36$)	**Number of pituitary surgeries per surgeon/year**	**Total number of pituitary surgeries at center** (single surgeon)
Klinikum Grosshadern, Munich	46 (38%)	8 (22%)	80–90	850
University of Erlangen-Nürnberg	19 (16%)	10 (28%)	250–300[a]	2000
University of Tuebingen	12 (10%)	2 (6%)	100	1100
Other centers	43 (36%)	16 (44%)		

[a]Number of pituitary surgeries per surgeon/year in University of Erlangen-Nürnberg since 2005.

Table 10: Neurosurgical centers, where 1st and 2nd TSS were performed. *Adapted from Dimopoulou et al., 2013.*

	All patients ($n=120$)
Gender	
Females	96 (80%)
Males	24 (20%)
Age (years) (mean (range))	50 (27–86)
Age at first diagnosis (years) (mean (range))	41 (9–78)
BMI (kg/m^2) (mean ± S.D.)	28 ± 7
Type of tumor (based on preoperative MRI)	
Macroadenoma	32 (27%)
Visible microadenoma	58 (48%)
No visible adenoma	30 (25%)
Cavernous sinus invasion (CSI)	13 (11%)
Macroadenoma	8 (7%)
Microadenoma	5 (4%)
Ethnicities/races	
Caucasian	120 (100%)
Preoperative laboratory values	
Serum cortisol 08.00 (μg/dl) (mean ± S.D.)	31 ± 26
UFC (μg/24 h) (mean ± S.D.)	430 ± 602
Plasma ACTH (pg/ml) (mean ± S.D.)	86 ± 73
Comorbidities	
Arterial hypertension	60 (50%)
Diabetes mellitus	22 (18%)
Dyslipidemia	20 (17%)
Osteoporosis	26 (22%)
Depression	26 (22%)
Mean follow-up for clinical data ± S.D. (months)	79 ± 67

Table 11: Baseline characteristics of the study population. *Adapted from Dimopoulou et al., 2013.*

Following primary surgery, the overall remission rate was 71% (n=120). A remission rate of 79% was accomplished in the microadenoma group (n=58), while in the macroadenoma group (n=32), remission rate after first TSS was 69%. In cases of no visible adenoma (n=30), remission rate was 57% (table 12). Mean follow-up after first TSS was 79±67 (range 252) months. After successful first TSS, overall recurrence rate was 34% (22% of patients with microadenoma, 59% of patients with macroadenoma and 35% of patients with no visible adenoma; p=0.007). Time to recurrence after first TSS ranged from 5 to 205 months (mean of 54±54 months).

Second TSS was considered in all cases of persistent or recurrent CD after first TSS (n=64), according to the current treatment algorithm for CD. Second TSS (n=28) was not performed in patients with ACTH-secreting macroadenomas with tumor invasion into the cavernous sinus or sphenoid (n=8), who might not benefit from a second operation, in case of patients' unwillingness to undergo second TSS (n=12) or other contraindications to surgery (n=8). Thirty-six of 120 CD patients (30%) underwent second TSS. Second TSS was carried out by the same surgeon, in the same neurosurgical center where first TSS took place in 64 % (23/36), suggesting patients' satisfaction. Overall remission rate of CD after second TSS was 42% (36% of patients with microadenoma, 29% of patients with macroadenoma and 75% of patients with no visible adenoma). Mean follow-up after second TSS was 62±54 (range 187) months. Overall recurrence rate after successful second TSS was 40% (40% of patients with microadenoma, 75% of patients with macroadenoma and 17% of patients with no visible adenoma). The time to recurrence after second TSS was shorter (mean 27±29, range 3 - 76 months).

	All patients	Macroadenoma	Microadenoma	No visible adenoma	*P* value
First TSS	*n*=120	*n*=32	*n*=58	*n*=30	
Remission	85 (71%)	22 (69%)	46 (79%)	17 (57%)	0.035
Disease persistence	35 (29%)	10 (31%)	12 (21%)	13 (43%)	0.082
Recurrence	29/85 (34%)	13/22 (59%)	10/46 (22%)	6/17 (35%)	0.007
Mean time to recurrence ±s.d. (months)	54±54	41±35	44±30	102±96	0.075
Second TSS	*n*=36	*n*=14	*n*=14	*n*=8	
Remission	15 (42%)	4 (29%)	5 (36%)	6 (75%)	0.124
Disease persistence	21 (58%)	10 (71%)	9 (64%)	2 (25%)	0.065
Recurrence	6/15 (40%)	3/4 (75%)	2/5 (40%)	1/6 (17%)	0.611
Mean time to recurrence ±s.d. (months)	27±29	35±36	15±16	120±0	0.522
Final follow-up	*n*=120	*n*=32	*n*=58	*n*=30	
Remission	110 (92%)	24 (75%)	56 (97%)	30 (100%)	0.000
Disease persistence	10 (8%)	8 (25%)	2 (3%)	0 (0%)	0.000

Table 12: Remission rates, disease persistence, recurrence rates and mean time to recurrence after first TSS, after second TSS and at final follow-up according to preoperative MRI. *Adapted from Dimopoulou et al., 2013.*

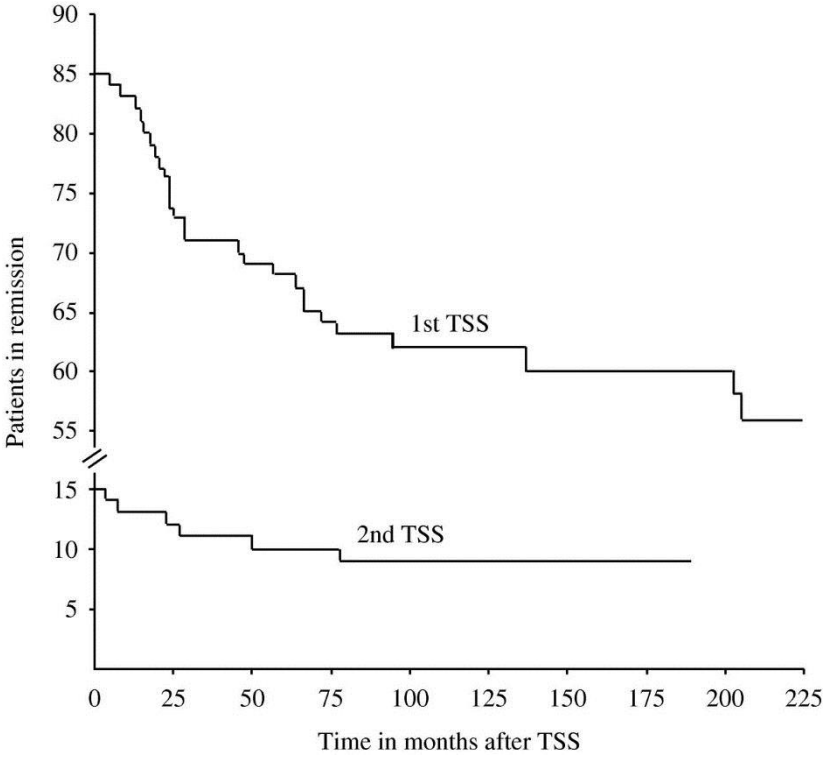


Figure 6: Kaplan–Meier curve showing freedom from recurrence of Cushing's disease in patients after successful first and/or second TSS. *Adapted from Dimopoulou et al., 2013.*

Within this study, 30 patients with no visible tumor on preoperative MRI underwent TSS; during surgery a pituitary adenoma was detected in 16/30 cases (53%). A systematic dissection of the pituitary gland was performed in the remaining cases (n=14); only one patient underwent total hypophysectomy. Of the 8 patients with no

visible tumor preoperatively, a pituitary adenoma was visualised during second TSS in 2/8 cases (25%). The remaining 6 patients received a systematic dissection of the pituitary gland; one patient received a hemi-hypophysectomy. In the cases where no definite tumor was not found during surgery, remission rates after first and second TSS were 50% and 100%, respectively.

There were no significant differences in remission and recurrence rates after first and after second TSS when comparing outcomes of each participating center (table 13).

	All patients	Klinikum Grosshadern Munich	University of Erlangen-Nürnberg	University of Tuebingen	*P* value
First TSS	*n*=77	*n*=46	*n*=19	*n*=12	
Remission	56 (72%)	35 (76%)	12 (63%)	9 (75%)	0.409
Disease persistence	21 (28%)	11 (24%)	7 (37%)	3 (25%)	0.557
Recurrence	13/56 (23%)	12/35 (34%)	1/12 (8%)	0/9 (0%)	0.061
Second TSS	*n*=20	*n*=8	*n*=10	*n*=2	
Remission	8 (40%)	3 (38%)	4 (40%)	1 (50%)	0.949
Disease persistence	12 (60%)	5 (62%)	6 (60%)	1 (50%)	0.949
Recurrence	2/8 (25%)	1/3 (33%)	1/4 (25%)	0/1 (0%)	0.870

Table 13: Remission rates, disease persistence and recurrence rates after first and after second TSS according to neurosurgical center. *Adapted from Dimopoulou et al., 2013.*

Postoperative hypocortisolism was diagnosed in all patients on biochemical testing while in hospital (serum cortisol <5ug/dL). 65/120 CD patients (54%) presented with postoperative hypocortisolism after first TSS (64% in the microadenoma group, 47% in the macroadenoma group and 43% in the group of no visible adenoma) (mean duration 45±60, range 252 months). Patients with postoperative hypocortisolism following first TSS were 0.7 times less likely to suffer disease recurrence than patients with postoperative eucortisolism (risk = 0.72; 95% confidence interval (CI) 0.60 – 0.88; Exact Sig. (2-sided) p=0.035). Longer duration of postoperative hypocortisolism did not prevent from CD recurrence (48±64. vs. 32±22 months; p=0.186). Overall frequency of postoperative hypocortisolism after second TSSwas 33% (12/36 patients) (36% in the microadenoma group, 29% in the macroadenoma group and 63% in the group of no visible adenoma) (mean duration 15±16, range 56 months). Postoperative

hypocortisolism after second TSS (risk = 0.83; 95% CI 0.25 – 2.73; Exact Sig. (2-sided) p=1.000), nor its longer duration (17±17 vs. 5 months; p=0.55) prevented patients from disease recurrence.

Of the 120 CD patients included in this analysis, 92% were in remission at final follow-up (100% in the group of no visible adenoma, 97% in the microadenoma and 75% in the macroadenoma group). Overall, 8% of the CD patients suffered from disease persistence at final follow-up (table 12). Nine patients were lost to follow up (n=8 after 1st TSS, n=1 after 2nd TSS).

Regarding pituitary deficiencies, 81 of 120 (68%) patients presented with deficiency of at least one pituitary hormone at final follow-up, with ACTH being influenced in most cases with 51% (isolated ACTH deficiency in 29%). Frequencies of LH/FSH, TSH and GH deficiencies accounted for 29%, 22% and 22%, respectively. Posterior pituitary deficiency was less frequent (8%).

Taken together, remission rates after first TSS in our series incorporating different neurosurgeons were comparable with available literature, whereas recurrence rates both after first and second TSS fell at the higher end of the published single-surgeon series so far, supporting our study hypothesis. Second TSS was responsible for long-term remission in additional 8% of the CD patients. Postoperative hypocortisolism after first TSS, though not its duration, was associated with a lower risk of CD recurrence. At final follow-up, hypopituitarism of any degree persisted in some patients.

5. Personality in Patients with Cushing's Disease

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. 2012 Apr 28. [Epub ahead of print]

Aim of this study was to verify the hypothesis that patients with CD show an anxiety-associated personality profile as well as to determine the effects of disease- and treatment-related factors that might contribute to these personality traits. We employed two standardized personality questionnaires, the Cloninger Personality Questionnaire (TPQ) and the short version of the revised Eysenck Personality Questionnaire-RK (EPQ-RK), in order to test this hypothesis. Additionally, we contrasted CD patients against a clinical control group with NFPA and age- and gender-matched mentally healthy controls to exclude the possibility that pituitary adenomas and/or their treatment are associated with anxiety associated personality traits.

	Mentally healthy controls (1)	NFPA (2)	CD (3)	Global test		p value (Bonferroni-Holm-corrected post hoc tests)		
				χ^2/ANOVA	p value	1 vs. 2	2 vs. 3	1 vs. 3
Gender								
Male	18 (18)	39 (65)	9 (18)					
Female	82 (82)	21 (35)	41 (82)	43.93	<0.001	<0.001	<0.001	n.s.
Age, years	46.36 ± 11.57	60.22 ± 10.61	46.36 ± 11.63	32.10 (ANOVA)	<0.001	<0.001	<0.001	n.s.
Primary adenoma type								
Macroadenoma	n.a.	50 (83)	10 (20)		<0.001		<0.001	
Microadenoma	n.a.	4 (7)	19 (38)					
Unknown size	n.a.	6 (10)	21 (42)					
Treatment								
Surgery	n.a.	52 (87)	49 (98)					
Radiotherapy	n.a.	15 (25)	13 (26)					
Medical therapy	n.a.	0	5 (10)					
Comorbidities								
Arrhythmias	0	3 (5)	9 (18)					
Cardiomyopathy	0	0	1 (2)					
Cerebrovascular disease	0	3 (5)	1 (2)					
Hypertension	16 (16)	27 (45)	30 (60)	35.01	<0.001	n.s.	<0.001	<0.001
Coronary artery disease	0	2 (3)	0					
Myocardial infarction	0	1 (2)	0					
Arthralgia	0	25 (42)	25 (50)					
Arthropathy	0	9 (15)	11 (22)					
Carpal tunnel syndrome	0	11 (18)	9 (18)					
Diabetes mellitus	2 (2)	6 (10)	11 (22)	17.48	<0.001	n.s.	0.038	<0.001
Pituitary deficiency	n.a.	45 (75)	32 (64)					
Hyperprolactinaemia	n.a.	2 (3.3)	0					
Sleep apnea	0	6 (10)	3 (6)					
Other lung diseases	0	1 (2)	3 (6)					
Malignancies	5 (5)	6 (10)	3 (6)					

Values are means ± SD or numbers with percentages in parentheses. n.s. = Nonsignificant; n.a. = not applicable.

Table 14: Demographic and clinical characteristics of the study groups. *Adapted from Dimopoulou et al., 2012.*

Patients with CD showed significantly less novelty seeking behaviour (TPQ-NS; p<0.001), which comprises low exploratory excitability (TPQ-NS1; p<0.001) and low extravagance (TPQ-NS3; p=0.015), compared to mentally healthy controls. Moreover, CD patients reported more anticipatory worries and pessimism (TPQ-HA1; p<0.001), higher fear of uncertainty (TPQ-HA2; p<0.001), shyness with strangers (TPQ-HA3; p<0.001), fatigability and asthenia (TPQ-HA4; p<0.001), indicating high harm avoidance (TPQ-HA; p<0.001). Overall, CD patients were not more reward dependent (TPQ-RD; p>0.05). We could not detect any significant differences between the two groups regarding sentimentality, persistence, attachment or dependence. As far as the three personality dimensions defined by Eysenck are concerned, CD patients were more neurotic (EPQ-N; p<0.001) and socially desirable (EPQ-SD; p=0.040), but less extraverted (EPQ-E; p=0.003), compared to a mentally healthy population.

We also documented elevated scores in harm avoidance (TPQ-HA; p<0.001), social desirability (EPQ-SD; p<0.001) and neuroticism (EPQ-N; p<0.001) in NFPA patients in comparison to mentally healthy controls. Results for novelty seeking (TPQ-NS) and extraversion (EPQ-E) were similar, whereas CD patients showed reduced scores on these scales when compared with mentally healthy controls. The highest scores regarding neuroticism (EPQ-N) were recorded in CD patients, followed by significantly lower scores in NFPA patients (p=0.003), which were still higher than those detected in mentally healthy controls (p<0.001).

	Mentally healthy controls (1)	NFPA (2)	CD (3)	ANCOVA		p value (Bonferroni-Holm-corrected post hoc tests)		
				F(2, 18)	p value	1 vs. 3	2 vs. 3	1 vs. 2
TPQ								
TPQ novelty seeking total (TPQ-NS)	16.45 ± 4.45	13.49 ± 4.83	13.74 ± 3.99	7.60	0.001	<0.001	n.s.	n.s.
TPQ harm avoidance total (TPQ-HA)	10.33 ± 5.48	15.63 ± 6.81	19.94 ± 6.69	35.36	<0.001	<0.001	n.s.	<0.001
TPQ reward dependence total (TPQ-RD)	17.32 ± 4.29	15.56 ± 3.69	17.44 ± 4.04	0.34	n.s.	n.s.	n.s.	n.s.
TPQ exploratory excitability (TPQ-NS1)	4.71 ± 1.71	3.65 ± 1.83	3.48 ± 1.75	6.83	0.001	<0.001	n.s.	n.s.
TPQ impulsiveness (TPQ-NS2)	3.87 ± 1.76	3.44 ± 2.12	3.30 ± 1.95	2.63	n.s.	n.s.	n.s.	n.s.
TPQ extravagance (TPQ-NS3)	4.31 ± 1.54	3.37 ± 1.50	3.74 ± 1.76	4.32	0.015	0.015	n.s.	n.s.
TPQ disorderliness (TPQ-NS4)	3.56 ± 1.68	3.00 ± 1.57	3.24 ± 1.36	0.87	n.s.	n.s.	n.s.	n.s.
TPQ anticipatory worries and pessimism (TPQ-HA1)	3.08 ± 2.12	4.25 ± 2.49	5.68 ± 2.19	22.95	<0.001	<0.001	n.s.	<0.001
TPQ fear of uncertainty (TPQ-HA2)	3.32 ± 1.87	4.40 ± 1.82	5.30 ± 1.62	15.15	<0.001	<0.001	n.s.	0.002
TPQ shyness with strangers (TPQ-HA3)	2.14 ± 1.71	2.82 ± 1.86	3.62 ± 1.69	8.95	<0.001	<0.001	n.s.	n.s.
TPQ fatigability and asthenia (TPQ-HA4)	1.78 ± 1.70	4.14 ± 2.66	5.34 ± 3.01	36.58	<0.001	<0.001	n.s.	<0.001
TPQ sentimentality (TPQ-RD1)	3.88 ± 1.23	3.95 ± 1.17	4.22 ± 0.86	1.79	n.s.	n.s.	n.s.	n.s.
TPQ persistence (TPQ-RD2)	3.74 ± 2.10	3.54 ± 1.86	4.24 ± 2.03	1.32	n.s.	n.s.	n.s.	n.s.
TPQ attachment (TPQ-RD3)	6.70 ± 2.64	5.70 ± 2.28	6.08 ± 2.30	0.90	n.s.	n.s.	n.s.	n.s.
TPQ dependence (TPQ-RD4)	3.00 ± 1.35	2.37 ± 1.41	2.92 ± 1.61	0.20	n.s.	n.s.	n.s.	n.s.
EPQ-RK								
EPQ-RK psychoticism (EPQ-P)	1.96 ± 1.68	1.34 ± 1.46	1.60 ± 1.46	1.24	n.s.	n.s.	n.s.	n.s.
EPQ-RK extraversion (EPQ-E)	7.55 ± 3.32	5.91 ± 3.84	5.32 ± 3.68	5.21	0.006	0.003	n.s.	n.s.
EPQ-RK neuroticism (EPQ-N)	2.84 ± 2.20	4.02 ± 2.80	6.48 ± 3.39	29.67	<0.001	<0.001	0.003	<0.001
EPQ-RK social desirability (EPQ-SD)	3.20 ± 2.42	5.76 ± 2.75	4.04 ± 2.42	7.40	0.001	0.040	n.s.	<0.001

Values are means ± SD. Results of the EPQ-RK and the TPQ are compared between groups using ANCOVA controlling for age, gender, arterial hypertension and diabetes mellitus. Bonferroni-Holm-corrected post hoc tests for two-group comparisons are performed in the case of significant differences in the global ANCOVA. n.s. = Nonsignificant.

Table 15: Personality traits of the study groups. *Adapted from Dimopoulou et al., 2012.*

Additionally, we applied ANCOVA controlling for age and gender, in order to assess personality differences between biochemically controlled and uncontrolled CD patients, between hypopituitary patients vs. patients with normal pituitary function, between radiated vs. non-radiated CD patients or dependent on disease duration (>median vs. <median). Moreover, we carried out a subgroup analysis in patients with

and without arthralgia, since chronic pain might be altering personality. Persistent hypercortisolemia was associated with significantly higher fear of uncertainty (TPQ-HA2; p=0.008), fatigability and asthenia (TPQ-HA4; p=0.034), indicating overall high harm avoidance (TPQ-HA; p=0.036) when contrasted to biochemically controlled CD. Besides, patients with hypopituitarism were more shy with strangers (TPQ-HA3; p=0.011) in comparison to patients with normal pituitary function.

In conclusion, a distinct pattern of personality traits associated with high anxiety in combination with traits of low externalizing behaviour is present in CD patients. This personality profile is comparable with acromegalic patients, but only partly with NFPA patients. Persistent hypercortisolemia and hypopituitarism, though not radiation therapy or duration of active hypercortisolism were partially associated with these personality traits. The reported personality pattern might constitute an additional challenge for diagnosis and therapy of CD and might contribute to impaired social and psychological functioning and well-being.

Discussion

The studies presented herein had as initiating point the need to further elucidate cardiometabolic and neuropsychiatric risk profile in patients with pituitary adenomas even after long-term biochemical control of the disease.

Regarding pain syndromes, a high prevalence of bodily pain and headache was documented in patients with pituitary adenomas *(Dimopoulou et al. 2014).* Although the causal connection between bodily pain and pituitary disease is not clear, we know e.g. that persistent GH excess in acromegaly can lead to arthropathy and arthralgia (*Biermasz et al., 2005*). The fact that CD patients are more susceptible to developing pain *(Dimopoulou et al. 2014)* is not surprising, since hypothalamo-pituitary-adrenal axis dysfunction has been suggested as a contributing factor to the development of chronic pain both in animal models and in clinical studies (*Alexander et al., 2009*). Modifiable factors such as tumor size, genetic predisposition, previous surgery, irradiation or medical therapy did not have significant influence neither on neuropathic pain nor on headache-related disability *(Dimopoulou et al. 2014)*, which rather suggests previous irreversible effects on the central nervous system leading to chronic pain.

One should also bear in mind that patients with pituitary adenomas not only suffer from pain syndromes, but additionally show decreased quality of life and sleep as well as increased rates of depression compared with matched controls. A significant proportion of the reduced quality of life can be attributed to the presence of depression and worse sleep quality *(Leistner et al. 2015).* These findings are comparable with previous results about QoL in patients with pituitary adenomas (*van der Klaauw et al., 2008*), as well as with results about subjective sleep quality of separate patient groups e.g. of acromegaly (*Copinschi et al., 2010*) or NFPAs (*Biermasz et al., 2010*).

The involvement of growth hormone and IGF-1 in the regulation of metabolism and body composition is well known. In a cross-sectional study, biochemically controlled patients with acromegaly were shown to have an adverse anthropometric risk profile, mainly due to elevated adiposity measurements *(Dimopoulou et al. 2010).* According to the literature, these findings can be attributed to a number of factors: Relative "overtreatment of acromegaly" might be resulting in relative growth hormone deficiency. *Schmid et al. 2006* have proposed other pituitary deficiencies as the underlying cause for an adverse anthropometric risk profile in acromegaly. Additionally, acromegalic patients are known to lack physical exercise because of persisting joint complaints or arthropathy (*Biermasz et al. 2005*), while medical treatment for acromegaly itself might also be responsible for increased measurements of body mass and body fat (*Plöckinger et al., 2008*).

Despite obvious external changes, diagnosis of acromegaly is often delayed long after disease onset. This hypothesis was, however, not confirmed by our findings, since body image perception of acromegalic patients did not differ from NFPA controls, who do not show physical/bodily changes. This lack of bodily self-perception was similar in patients with different disease severity, different duration of hormonal excess or biochemical control, but correlated to depression (*Dimopoulou et al., 2016*). These findings are in accordance with previous studies reporting disturbed body image in acromegalic patients (*Ezzat, 1992; Pantanett et al., 2002*). These results also correspond to our previous work, showing that patients with acromegaly burden high neuropsychiatric morbidity including high prevalence of affective disorders (*Sievers et al., 2009*), macroscopic brain architecture changes (*Sievers & Samann et al., 2009*), anxiety-related personality traits (*Sievers et al., 2009*), cognitive dysfunction (*Sievers et al., 2012)* and pain syndromes (*Dimopoulou et al., 2014*). Tiemensma et al. have also

documented affected illness perceptions in acromegalic patients even after long-term remission of the disease (*Tiemensma et al., 2011*) and recently, increased psychosocial impairment has been linked to diagnostic delay in acromegaly (*Siegel et al., 2013*). However, emotional disorders do not seem to burden only acromegalic patients, but also patients with other types of pituitary adenomas, affecting the diagnostic process, as seen in our NFPA controls (*Flitsch et al., 2000*).

Furthermore, we showed that except for traditional remission criteria for acromegaly such as biochemical variables, modifiable factors e.g. depression and anxiety are superior over biochemical control in predicting quality of life and might provide valuable targets for possible future treatment interventions (*Geraedts et al. 2015).*

TSS presents the treatment of choice for CD, caused by an ACTH-secreting pituitary adenoma. Remission and recurrence rates are dependent on tumor size, extension, adenoma visibility on MRI and neurosurgical expertise. In our series incorporating different neurosurgeons in the Munich Metropolitan Region, we reported - against our study hypothesis - an overall remission rate of 71% after first TSS, comparing favourably with the literature (*Tritos et al., 2011*). The high disease persistence as well as high recurrence rates identified both after first and after second TSS, might be attributed to the fact that our endocrinology departments serve as referral centers for difficult, complicated cases. Postoperative hypocortisolism following first TSS was associated with a lower risk of suffering disease recurrence, as has been shown in the literature by *Patil et al. 2008*. Second TSS, which should be considered in patients with refractory or recurrent CD, led an additional 8% of the patients to long-term CD remission; at this point, we have to take into account that we reported not on a single-, but on a multiple-surgeon series involving different neurosurgical skills and reflecting care reality in the Munich Metropolitan Region *(Dimopoulou et al. 2013).*

Chronic hypercortisolism has been suggested to contribute to an altered personality profile in patients with CD. In our series, CD patients were characterized by elevated anxiety-related personality traits, harm avoidance and neuroticism, combined with reduced scores in externalizing traits, novelty seeking and extraversion. This pattern has been previously recorded by our group in acromegaly (*Sievers et al., 2009*), while NFPA patients serving as clinical control group described themselves by lower - though still elevated - neuroticism scores. Our results were comparable with the findings by *Tiemensma et al., 2010*, who documented "maladaptive" traits even after long-term cure of CD. In agreement with these findings, we observed elevated scores in anxiety-related traits as well as reduced scores in externalizing traits, which corresponds to higher scores on social avoidance as reported by *Tiemensma et al., 2010*. Persistent cortisol excess correlated - as expected - with anxiety-related personality traits including higher scores on harm avoidance in total, but also on the subscales fear of uncertainty and fatigability and asthenia *(Dimopoulou et al. 2013).*

Summary and Conclusions

Summarizing, the studies described herein have contributed to understanding that patients with hormonal excess syndromes show a persistent unfavorable cardiometabolic and neuropsychiatric risk profile even after long-term biochemical control of the disease. Impaired quality of life persists as a remaining effect of long-standing hormonal excess. Despite advanced neurosurgical expertise and evoking therapy regimens over the years, hormonal excess syndromes represent due to high recurrence and persistence rates an ongoing challenge for the treating physicians/ endocrinologists and require complex interdisciplinary approach and multimodal treatment strategies to be able to treat these patients properly. Our findings suggest that neuropsychiatric assessment should be integrated in the diagnostic and therapeutic work-up of patients with hormonal excess syndromes in order to treat them appropriately and improve their quality of life. Neuropsychiatric changes should be taken into account when treating such patients, as they might interfere with the patient-physician communication and/or challenge the patients' social and psychological functioning. Due to the lack of large patient cohorts with available biomaterial, structured patient registries and consultation hours are needed in order to develop personalized therapy strategies for these patients. Additionally, randomized studies with a prospective design are necessary to be able to draw conclusions between the causal relationship of hormonal excess syndromes and associated changes and the development of a cardiovascular and neuropsychiatric risk profile.

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