Aus dem Max-Planck-Institut für Psychiatrie
Direktor: Prof. Dr. Dr. Martin E. Keck
sowie dem Zentrum für endokrine Tumore der Ludwig-Maximilians-Universität München
Direktor: Prof. Dr. Martin Reincke

Psychiatric symptoms in patients with pituitary adenomas: the role of sleep quality, depression and quality of life

Dissertation

zum Erwerb des Doktorgrades der Humanbiologie
an der Medizinischen Fakultät der
Ludwig-Maximilians-Universität zu München

vorgelegt von
Sarah Miriam Leistner

aus
München

2019

Mit Genehmigung der Medizinischen Fakultät

der Universität München

Berichterstatter:	Prof. Dr. Günter K. Stalla
Mitberichterstatter:	Prof. Dr. Christoph J. Lauer
	PD Dr. Cornelius Schüle
Mitbetreuung durch die promovierte Mitarbeiterin:	PD Dr. Caroline Sievers
Dekan:	Prof. Dr. med. dent. Reinhard Hickel

Tag der mündlichen Prüfung: 25.11.2019

Eidesstattliche Versicherung

Leistner, Sarah Miriam

Ich erkläre hiermit an Eides statt, dass ich die vorliegende Dissertation mit dem Thema „**Psychiatric symptoms in patients with pituitary adenomas – the role of sleep quality, depression and quality of life“** selbständig verfasst, mich außer der angegebenen keiner weiteren Hilfsmittel bedient und alle Erkenntnisse, die aus dem Schrifttum ganz oder annähernd übernommen sind, als solche kenntlich gemacht und nach ihrer Herkunft unter Bezeichnung der Fundstelle einzeln nachgewiesen habe.

Ich erkläre des Weiteren, dass die hier vorgelegte Dissertation nicht in gleicher oder in ähnlicher Form bei einer anderen Stelle zur Erlangung eines akademischen Grades eingereicht wurde.

München, 07.06.2018 Sarah Miriam Leistner

INHALTSVERZEICHNIS

1. ABKÜRZUNGSVERZEICHNIS

BDI	Beck-Depressions-Inventar
DETECT	Diabetes Cardiovascular Risk-Evaluation: Targets and Essential Data for Commitment of Treatment
DSQ	Depression-Screening Questionnaire
EQ-5D	Euro-Quol (5 Dimensionen)
FBeK	Fragebogen zur Beurteilung des eigenen Körpers
FKB-20	Fragebogen zum Körperbild
GH	Growth Hormone
IGF-1	Insulin-like growth factor 1
LMU	Ludwig-Maximilians-Universität, München
MPI	Max-Planck-Institut für Psychiatrie, München
PSQI	Pittsburgh Sleep Quality Index
PTBS	Posttraumatische Belastungsstörung
VAS	Visual Analog Scale

2. PUBLIKATIONSLISTE (bis 2016)

Publikationen

Dimopoulou C, Leistner SM, Ising M, Schneider HJ, Schopohl J, Rutz S, Kosilek R, Frohner R, Stalla GK, Sievers C (2016). *Body Image Perception in Acromegaly is Not Associated with Objective Acromegalic Changes, But Depends on Depressive Symptoms.* Neuroendocrinology.

Leistner SM, Klotsche J, Dimopoulou C, Athanasoulia AP, Roemmler-Zehrer J, Pieper L, Schopohl J, Wittchen HU, Stalla GK, Fulda S, Sievers C (2015). *Reduced sleep quality and depression associate with decreased quality of life in patients with pituitary adenomas.* European Journal of Endocrinology.

Fodor KE, Unterhitzenberger J, Chou CY, Kartal D, Leistner S, Milosavljevic M, Nocon A, Soler L, White J, Yoo S, Alisic E (2014). *Is traumatic stress research global? A bibliometric analysis.* European Journal of Psychotraumatology. (Note: authors Chou, Corbella, Kartal, Leistner, Milosavljevic, Nocon, White and Yoo have contributed equally.)

Posterpräsentationen

Leistner SM, Dimopoulou C, Athanasoulia AP, Roemmler-Zehrer J, Schopohl J, Stalla GK, Sievers C (2015, March). *State- and trait-anxiety in patients with pituitary adenomas.* Poster auf dem 58. Symposium der Deutschen Gesellschaft für Endokrinologie (DGE), Lübeck.

Leistner SM, Mestel R, Rosner R (2013, June). *Attachment Styles in Post-traumatic Stress Disorder (PTSD).* Poster presented at the XIII ESTSS conference "Trauma and its clinical pathways: PTSD and beyond", Bologna.

Leistner SM, Klotsche J, Dimopoulou C, Athanasoulia AP, Pieper L, Wittchen HU, Stalla GK, Sievers C* & Fulda S* (2011, November), *The role of depression for quality of life and sleep in patients with pituitary dysfunction.* Poster auf der 15. Jahrestagung der Sektion Neuroendokrinologie der Deutschen Gesellschaft für Endokrinologie (DGE), Frankfurt am Main.

3. EINLEITUNG

Eine Metaanalyse aus dem Jahr 2004, die in ihre Berechnungen alle bis 2000 über MEDLINE recherchierbaren englischsprachigen und die Einschlusskriterien erfüllende Artikel einbezog, ermittelte für Hypophysenadenome eine Prävalenzrate von 16,7% (Ezzat et al., 2004). Bei 84,6% der Tumore an Hypophyse oder in der Sellar-Region handelt es sich laut dem Deutschen Register für Hypophysentumoren in einer Erhebungszeitraum von 1996 bis 2005 um Hypophysenadenome (Saeger et al., 2007). Fernandez und Kollegen (2010) zeigen in ihren Daten, dass es sich dabei am häufigsten um Prolaktinome, in absteigender Häufigkeit um hormonell-inaktive Adenome, Akromegalie sowie Morbus Cushing handelt, bei Frauen Prolaktinome (76%), bei Männern hingegen die hormon-inaktiven Adenome (57%) am häufigsten auftreten. McDowell und Kollegen (2011) berichten aus ihrem Erhebungszeitraum von 2004 bis 2007 in den USA, dass die Inzidenzrate für Hypophysenadenome mit dem Alter steigt, wobei Frauen früher in ihrem Leben betroffen seien. Männer bekämen ihre Diagnose meist später gestellt und weisen im Durchschnitt eine höhere Tumorgröße auf als Frauen.

In den letzten Jahren sind zahlreiche Studien zu verschiedenen Symptomen von Hypophysenadenomen veröffentlicht worden. Immer stärker in den Vordergrund sind dabei besonders auch psychische Symptome getreten, was wenig verwunderlich und dringend notwendig erscheint. Patienten mit Hypophysenadenom zeigen neben zahlreichen somatischen Begleitsymptomen (z.B. Allolio & Schulte, 2010) häufig beispielweise Schmerzsymptome (z.B. Dimopoulou et al., 2014) oder neuropsychiatrische Symptome (z.B. S. Leistner et al., 2015; siehe Poster Anhang; für Patienten mit Morbus Cushing z.B. Pereira, Tiemensma, & Romijn, 2010).

Anders herum erhält interessanterweise auch in der psychiatrischen Forschung der endokrinologische Blickwinkel bei vielen Störungsbildern einen immer wichtigeren Stellenwert, so finden sich beispielsweise einige Studien zur Posttraumatischen Belastungsstörung (PTBS): Ein interessanter Befund aus den letzten Jahren betont dabei die

Wichtigkeit der Hypophysen-Hypothalamus-Achse und zeigt auf, dass das akute Cortisol-Level sowie das Dehydroepiandrosteron-Level die Symptome einer PTBS bei Überlebenden eines kürzlich vorgefallenen traumatischen Erlebnisses vorhersagen können (z.B. Mouthaan et al., 2014).

Die vorliegende Promotionsarbeit stellt neben der Depressivität und Schlafqualität insbesondere die Lebensqualität von Patienten mit Hypophysenadenom in den Vordergrund. Ebenso betrachtet sie die Körperbildwahrnehmung von Akromegalie-Patienten.

Gemeinsam ist den vorliegenden Veröffentlichungen als übergeordnetes Thema die Fokussierung auf psychiatrische Symptome bei Patienten mit Hypophysenadenom. So soll die Arbeit einen Beitrag bei der Schließung offener Fragestellungen bezüglich psychischer Begleit- oder Folgesymptome leisten. Gemeinsam ist beiden Veröffentlichungen damit aber auch, dass sie eine zentrale Grundlage für die Entwicklung einer optimierten Behandlung dieser Erkrankungsbilder darstellen. In diesem Zusammenhang können Befunde über Symptome, die die Lebensqualität von Patienten mit Hypophysenadenom beeinflussen, ebenso hilfreich sein wie Erkenntnisse über den Zusammenhang eines negativen Körperbildes mit psychiatrischen Symptomen bei Patienten mit Akromegalie.

3.1. Theoretischer Hintergrund und Fragestellung Veröffentlichung I

Einige Studien haben bereits von einer reduzierten Lebensqualität für Patienten mit Hypophysenadenom berichtet (z.B. van der Klaauw, Kars, et al., 2008; Biermasz et al., 2004; Webb, 2006), auch Jahre nach einer Operation oder einer hormonellen Einstellung (z.B. Johnson, Woodburn, & Vance, 2003; Paisley et al., 2007; Heald et al., 2004; van Aken et al., 2005).

Ebenso finden sich Befunde für eine reduzierte Schlafqualität – zum Zeitpunkt der Erarbeitung der Fragestellung der ersten Veröffentlichung überwiegend für Akromegalie und hormoninaktive Adenome (z.B. Copinschi et al., 2010; van der Klaauw, Pereira,

van Kralingen, Rabe, & Romijn, 2008; van der Klaauw, Biermasz, et al., 2008; Biermasz et al., 2011).

Für Patienten mit Akromegalie (z.B. Sievers et al., 2009; Tiemensma, Biermasz, van der Mast, et al., 2010) sowie insbesondere für Morbus Cushing-Patienten (z.B. Kelly, 1996; Sonino, Fallo, & Fava, 2010; Tiemensma, Biermasz, Middelkoop, et al., 2010; Pereira et al., 2010; Dimopoulou et al., 2013) zeigen sich deutlich erhöhte Prävalenzraten für depressive bzw. affektive Störungen. Die Studienlage bei Prolaktinom-Patienten sowie Patienten mit hormoninaktiven Adenomen lässt noch keine eindeutige Aussage zu, zufriedenstellende Untersuchungen zur Depressivität bei diesen Patientengruppen fehlen.

Eine der Fragestellungen der ersten Veröffentlichung untersucht die Lebensqualität, Depressivität und Schlafqualität bei allen vier Patientengruppen – auch um bisherige Forschungslücken zu schließen. Zudem erschien es uns - gerade vor dem Hintergrund, dass Patienten mit Hypophysenadenom noch Jahre nach ihrer somatischen Behandlung eine deutlich reduzierte Lebensqualität aufweisen – sehr wichtig, den Einfluss der Schlafqualität und der Depressivität auf die Lebensqualität bei Patienten mit Hypophysenadenom zu betrachten, zumindest soweit dies aus methodischer Sicht mit Daten einer Querschnittserhebung möglich ist. Diese Ergebnisse könnten einen ersten wichtigen Hinweis auch für die Entwicklungen von neuen Behandlungsalgorithmen dieser Patienten liefern und die Wichtigkeit von psychiatrischen und / oder psychotherapeutischen Bausteinen bei der optimierten Versorgung von Patienten mit Hypophysenadenom betonen.

3.2. Theoretischer Hintergrund und Fragestellung Veröffentlichung II

Akromegalie – verbunden mit einer übermäßigen GH-Ausschüttung – ist eine Erkrankung, die mit vielen äußeren körperlichen Veränderungen, z.B. Wachstum der Akren, einem Vorbiss, einer Makroglossie und einer Hypertrochosis einhergehen kann (Melmed, 2006). Trotz dieser deutlich sichtbaren Veränderungen wird die Diagnose

meist erst mit eindrücklicher Verspätung von durchschnittlich 6,6 bis 10,2 Jahren gestellt, was zu einer erhöhten Morbilität und Mortalität führt (z.B. Holdaway & Rajasoorya, 1999). Bisherige Studien haben bereits über eine gestörte Körperbildwahrnehmung bei Patienten mit dieser Erkrankung berichtet (z.B. Ezzat, 1992; Pantanetti, Sonino, Arnaldi, & Boscaro, 2002). Wie im Rahmen der ersten Veröffentlichung bereits beschrieben, leiden sie aber auch unter erhöhten Prävalenzraten für depressive Störungen. Zudem ist bekannt, dass ein chronischer GH/IGF-1-Exzess zu irreversiblen Veränderungen im zentralen Nervensystem führen kann, der mit Veränderungen in der makroskopischen Gehirnstruktur und mit einer Verschlechterung der kognitiven Leistungsfähigkeiten einhergehen kann (z.B. Leon-Carrion et al., 2010; Sievers et al., 2012).

In der zweiten Veröffentlichung untersuchten wir daher zum einen, ob sich die Körperwahrnehmung von Patienten mit Akromegalie von der von Patienten mit hormoninaktivem Adenom, die an keinen körperlichen Veränderungen leiden, unterscheidet. Eine Hypothese dabei ist, dass Akromegalie-Patienten subjektiv die Veränderungen nicht wahrnehmen können, obwohl sie objektiv bereits vorliegen. Diese Unfähigkeit, physische Veränderungen zu erkennen, mag einen Beitrag zu den sehr späten Diagnosestellungen leisten. Zum anderen wollten wir den Zusammenhang zwischen einem negativen Körperbild mit objektivierbaren Akromegalie-typischen Veränderungen, die von medizinischen Experten beurteilt wurden, ebenso wie zu potentiell daraus resultierenden Faktoren, wie z.B. psychiatrischen Auffälligkeiten (Depression, kognitive Einschränkungen), betrachten.

3.3. Beitrag zu den verfassten Fachartikeln

Der Beitrag bei der ersten Veröffentlichung erstreckt sich von der Mitentwicklung des Konzeptes und der Fragestellung sowie der eigenständigen Literaturrecherche, der selbstständigen Auswertung der Daten und Interpretation der Ergebnisse bis zur Anfertigung des vorliegenden Manuskriptes. Dabei stellten die statistischen Kenntnisse

mit der Verwendung gemischt-linearer Modelle mit Sicherheit die größte Herausforderung dar.

Bei der zweiten Veröffentlichung lag der Schwerpunkt meines Beitrages auf der Mitentwicklung der Fragestellung, der eigenständigen Auswertung der Daten und Interpretation der Ergebnisse sowie auf dem Verfassen von Ergebnisteil und Teilen des Diskussionsteils. Ebenso war die kritische Durchsicht des Manuskripts Teil meiner Mitarbeit an der vorliegenden Veröffentlichung.

Ausführlichere Hinweise zu den Beiträgen der einzelnen Co-Autoren sind Kapitel 2 zu entnehmen.

4. ZUSAMMENFASSUNG

4.1. Zusammenfassung (Deutsch): S. M. Leistner et al., 2015 & Dimopoulou et al., 2017

Hintergrund:

Patienten mit Hypophysenadenom leiden häufig unter zahlreichen psychischen Begleit- oder Folgesymptomen. Auch Jahre nach einer Operation oder einer hormonellen Einstellung zeigt sich eine reduzierte Lebensqualität. Ebenso finden sich Befunde für eine reduzierte Schlafqualität oder erhöhte Depressivität bei einzelnen Erkrankungsbildern. Studien berichten von einer gestörten Körperbildwahrnehmung bei Patienten mit Akromegalie oder auch von einer Verschlechterung des kognitiven Leistungsniveaus.

Fragestellungen:

Die vorliegende Dissertation untersuchte verschiedene psychiatrische Symptome bei Patienten mit Hypophysenadenom. Im Fokus standen dabei zum einen die Schlafqualität, Depressivität und Lebensqualität von Patienten mit Akromegalie, Morbus-Cushing, Prolaktinom oder hormoninaktiven Adenom, mit dem Ziel, vorhandenen Forschungslücken zu schließen, aber auch den Einfluss der Schlafqualität und Depressivität auf die Lebensqualität dieser Patientengruppen näher zu beleuchten. Zum anderen galt es, die Körperwahrnehmung von Patienten mit Akromegalie zu untersuchen und Zusammenhänge zwischen einem negativen Körperbild und objektivierbaren Akromegalie-typischen Veränderungen sowie zu potentiell daraus resultierenden Faktoren, wie z.B. psychiatrischen Auffälligkeiten (Depression, kognitive Einschränkungen), zu betrachten.

Design und Methoden:

Bei beiden Studien handelt es sich um Querschnittsuntersuchungen. Im Rahmen der ersten Studie wurden Patienten mit Hypophysenadenom (n=247), die sich in der en-

dokrinologischen Ambulanz des Max-Planck-Instituts für Psychiatrie (MPI) in München oder der Arbeitsgruppe Neuroendokrinologie der Ludwig-Maximilians-Universität (LMU) München vorstellten, mit Kontrollprobanden (n=757) aus der DETECT-Studie, einer großen epidemiologischen Studie mit Hausarztpatienten der Technischen Universität Dresden – zugeordnet nach Alter und Geschlecht - verglichen. Im Rahmen der zweiten Studie wurden Akromegalie-Patienten (n=81), eine Kontrollgruppe bestehend aus Patienten mit hormoninaktivem Adenom (n=60) – beide vorstellig am MPI oder der LMU - sowie Normwerte aus den Manualen der jeweiligen Untersuchungsinstrumente betrachtet.

In beiden Untersuchungen kamen in der Forschung bereits etablierte Fragebögen zum Einsatz. So wurde in der ersten Studie die Schlafqualität mit dem Pittsburgh Sleep Quality Index (PSQI), die Lebensqualität mit dem EQ-5D (u.a. bestehend aus einer visuellen Analog-Skala) sowie die Depressivität mit dem Beck-Depressions-Inventar (BDI) bzw. dem Depression Screening Questionnaire (DSQ) erhoben. In der zweiten Studie kamen der Fragebogen zum Körperbild (FKB-20) sowie der Fragebogen zur Beurteilung des eigenen Körpers (FBeK), das Beck-Depressions-Inventor (BDI) ebenso wie ein Expertenurteil und die Ergebnisse einer neuropsychologischen Testung bezüglich Aufmerksamkeit, Gedächtnis und exekutive Funktionen zum Einsatz. Komorbiditäten, biochemische Variablen oder bestimmte Tumorcharakteristiken wurden im Rahmen eines Interviews, einer somatischen Untersuchung oder mithilfe von Laborwerten erhoben.

Ergebnisse:

Patienten mit Hypophysenadenom zeigten eine reduzierte Lebensqualität und Schlafqualität, ebenso erhöhte Depressionswerte im Vergleich zu den Kontrollprobanden. Ein entscheidender Anteil der reduzierten Lebensqualität war mit dem Vorhandensein einer Depression oder einer reduzierten Schlafqualität verbunden. Patienten mit Akromegalie zeigten ein negativeres Körperbild verglichen mit Kontrollprobanden.

Die Depressivität hing dabei mit dem negativen Körperbild zusammen, keine Korrelation fand sich jedoch zwischen einem negativen Köperbild und zu von Experten eingeschätzten objektiven äußerlichen Veränderungen oder kognitiven Leistungseinschränkungen.

Schlussfolgerung:

Die Befunde betonen zum einen die Wichtigkeit, depressive Symptome und Schlafstörungen bei Patienten mit Hypophysenadenom zu diagnostizieren, da sie einen Einfluss auf die reduzierte Lebensqualität dieser zu haben scheinen. Zudem zeigt sich, dass das negative Körperbild bei Patienten mit Akromegalie zwar unabhängig von ihrer objektiven Erscheinung zu sein mag, die Depressivität jedoch mit einem negativen Körperbild einhergeht. In jedem Fall sollen die Ergebnisse zur Entwicklung einer optimierten und individualisierten Behandlung dieser Erkrankungsbilder beitragen, in denen ggf. auch psychiatrische und psychotherapeutische Ansätze eine Rolle spielen sollten.

4.2. Summary (English): S. M. Leistner et al., 2015 & Dimopoulou et al., 2017

Objectives:

Several studies have reported different psychiatric symptoms in patients with pituitary adenomas, even when patients doing well from a biochemical point of view or after somatic treatment. There are several findings of a reduced quality of life in these patient groups. Additionally, reduced quality of sleep or increased rates of depression have been observed for single patient groups with pituitary adenomas. Moreover, patients with acromegaly show disturbed body image perception and cognitive impairments.

This thesis considered different psychiatric symptoms in patients with pituitary adenomas. One focus should be the sleep quality, depression and quality of life in patients with acromegaly, Cushing's disease, prolactinomas and non-functioning pituitary adenomas with the aim to close gaps in research. Furthermore, we wanted to investigate the influence of sleep quality and depression on quality of life in these patients. Another focus should concentrate on the disturbed body image perception in patients with acromegaly or further their cognitive declines.

Design and methods:

In both cases the design was a cross-sectional study. In the first study we investigated patients with pituitary adenomas (n=247, from the Endocrine Outpatient Unit of the Max Planck Institute of Psychiatry, Munich, and the Department of Internal Medicine, Ludwig-Maximilians-University, Munich) and controls (n=757, from the DETECT cohort, a large epidemiological study in primary care patients of the Institute of Clinical Psychology and Psychotherapy, Technical University, Dresden) matched individually by age and gender. In the second study we considered patients with acromegaly (n=81) as well as a clinical control group of patients with nonfunctioning pituitary adenomas (n=60) – both from the Endocrine Outpatient Unit of the Max Planck Institute of Psychiatry, Munich, and the Department of Internal Medicine, Ludwig-Maximilians-University, Munich – and norm values of healthy controls.

We used standardized questionnaires: Sleep quality was assessed with the Pittsburgh Sleep Quality Index (PSQI) and QoL was measured by the generic EQ-5D and calculated by the time trade-off- and VAS-method. Depression was categorized as "no depression", "subclinical depression", and "clinical depression" according to the Beck Depressions Inventory (BDI) for patients and the Depression Screening Questionnaire (DSQ) for control subjects. Perceived body image was investigated with the Fragebogen zum Körperbild (FKB-20) and Fragebogen zur Beurteilung des eigenen Körpers (FBeK). We further evaluated body image in relation to objective acromegalic changes as judged by medical experts and psychiatric pathology, e.g. cognitive impairment by neuropsychological tests. Comorbidities, biochemical variables or tumour characteristics were assessed via interview, physical examination and laboratory analyses.

Results:

Patients with pituitary adenomas showed decreased quality of life and sleep quality as well as increased rates of depression compared with their matched control subjects. We have shown that a substantial proportion of the reduced quality of life was due to the incidence of depression and reduced sleep quality. Patients with acromegaly did not lack subjective perception of the disease state; they showed more negative body image, less vitality, more insecurity/paresthesia and more accentuation of the body compared to normal controls. Depression correlated with worse body image. No association were found between body image and objective acromegalic changes as judges by medical experts, cognitive decline or treatment status.

Conclusions:

On the one hand, the findings emphasize the importance of diagnosing depressive symptoms and sleep disturbances in patients with pituitary disease, with the ultimate goal to improve quality of life in patients with pituitary adenomas. Besides - even though negative body image in acromegalic patients is unrelated to their objective appearance and similar to those of nonfunctioning pituitary adenomas patients without major bodily changes – depression contributes to negative body image. On the other

hand, the results of both studies should add to an optimized and individualized treatment of these diseases possibly also psychotherapeutic approaches play a role.

5. VERÖFFENTLICHUNG I

Reduced sleep quality and depression associate with decreased quality of life in patients with pituitary adenomas

Sarah M Leistner[1], Jens Klotsche[2,5], Christina Dimopoulou[1], Anastasia P Athanasoulia[1], Josefine Roemmler-Zehrer[3], Lars Pieper[2], Jochen Schopohl[3], Hans-Ulrich Wittchen[2], Günter K Stalla[1], Stephany Fulda[1,4,*] and **Caroline Sievers[1,*]**

[1]Department of Endocrinology, Max-Planck-Institute of Psychiatry, Kraepelinstraße 2-10, 80804 Munich, Germany, [2]Institute of Clinical Psychology and Psychotherapy, Center of Clinical Epidemiology and Longitudinal Studies (CELOS), Technische Universität Dresden, Chemnitzer Straße 46, 01187 Dresden, Germany, [3]Medizinische Klinik Innenstadt, Ludwig-Maximilians University, Ziemssenstraße 1, 80336 Munich, Germany, [4]Sleep and Epilepsy Center, Neurocenter of Southern Switzerland, Civic Hospital (EOC) of Lugano, Via Tesserete 46, 6900 Lugano, Switzerland and [5]A Leibnitz Institute, German Rheumatism Research Center, Charitéplatz 1, 10117 Berlin, Germany
[*](S Fulda and C Sievers share senior authorship)

Correspondence should be addressed to S M Leistner
Email
sarah_leistner@psych.mpg.de

European Journal of Endocrinology

Abstract

Objectives: Several studies reported decreased quality of life (QoL) and sleep as well as increased rates of depression for patients with pituitary adenomas. Our aim was to explore to what extent differences in depression and sleep quality contribute to differences in QoL between patients with pituitary adenomas and controls.
Design: A cross-sectional case–control study.
Setting: Endocrine Outpatient Unit of the Max Planck Institute of Psychiatry, Munich, Department of Internal Medicine, Ludwig-Maximilians-University, Munich, and the Institute of Clinical Psychology and Psychotherapy, Technical University, Dresden.
Participants: Patients with pituitary adenomas ($n=247$) and controls (from the DETECT cohort, a large epidemiological study in primary care patients) matched individually by age and gender ($n=757$).
Measurements: Sleep quality was assessed with the Pittsburgh Sleep Quality Index (PSQI) and QoL was measured by the generic EQ-5D and calculated by the time trade-off- and VAS-method. Depression was categorized as 'no depression', 'subclinical depression', and 'clinical depression' according to the Beck Depressions Inventory for patients and the Depression Screening Questionnaire for control subjects.
Statistical analyses: General linear and generalized, logistic mixed models as well as proportional odds mixed models were calculated for analyzing differences in baseline characteristics and in different subgroups.
Results: Patients with pituitary adenomas showed decreased QoL (VAS index: 0.73 ± 0.19) and sleep (PSQI score: 6.75 ± 4.17) as well as increased rates of depression (subclinical or clinical depression: 41.4%) compared with their matched control subjects (VAS index: 0.79 ± 0.18, PSQI score: 5.66 ± 4.31, subclinical or clinical depression: 25.9%). We have shown that a substantial proportion of the reduced QoL (48% respectively 65%) was due to the incidence of depression and reduced sleep quality.
Conclusions: These findings emphasize the importance of diagnosing depressive symptoms and sleep disturbances in patients with pituitary disease, with the ultimate goal to improve QoL in patients with pituitary adenomas.

European Journal of Endocrinology (2015) **172**, 733–743

www.eje-online.org
DOI: 10.1530/EJE-14-0941

Published by Bioscientifica Ltd.

Introduction

Several studies have reported decreased quality of life (QoL) for patients with pituitary adenomas such as acromegaly, Cushing's disease, prolactinomas, and nonfunctioning pituitary adenomas (NFPAs). Van der Klaauw *et al.* (1) compared QoL in patients with different pituitary adenomas and showed disease-specific impairments in QoL for patients with acromegaly, Cushing's disease, prolactinomas, and NFPAs. Perceived QoL was especially decreased in treated patients with acromegaly compared with treated patients with NFPAs or prolactinomas. Biermasz *et al.* (2) showed that patients with acromegaly have persistently reduced QoL despite long-term biochemical cure of growth hormone (GH) excess. Furthermore, Webb (3) concluded that not only biochemical and radiological parameters should be evaluated in acromegaly since QoL was affected even in patients with controlled disease. Even though, as has been shown by Johnson *et al.* (4) or Paisley *et al.* (5), both insulin-like growth factor 1 (IGF1) levels and QoL scores improve with treatment, QoL levels remain reduced compared with age- and gender-matched controls. For Cushing's disease, previous studies demonstrated similar results with decreased QoL, even when patients are doing well from a biochemical point of view (e.g. (6, 7)). Kars *et al.* (8) showed that the QoL is impaired in female patients treated for microprolactinomas, especially due to increased anxiety and depression. Finally, Naliato *et al.* (9) confirmed the results, further reporting that the impaired QoL was inversely associated with prolactin (PRL) levels.

Besides the widely documented decreased QoL in patients with pituitary adenomas, also a decreased quality of sleep has been reported. Copinschi *et al.* (10) reported decreased sleep quality for patients with untreated acromegaly as well as decreased QoL, and assumed that disturbed sleep is likely to be partly responsible for increased tiredness. Even in patients with long-term biochemical remission of acromegaly, increased daytime sleepiness was observed. Patient's sleep duration and timing of sleep did not differ from healthy controls (11). Frieboes *et al.* (12) showed increased slow-wave sleep for patients with prolactinomas compared with a control group. Nevertheless, data on subjective sleep quality in these patients are still missing as is the case for patients with Cushing's disease. In addition, Van der Klaauw *et al.* (13) concluded that patients cured from craniopharyngiomas or nonfunctioning macroadenomas suffered from increased daytime somnolence despite normal sleep patterns (onset, sleep timing, duration, and rise time) compared with healthy controls. Furthermore, Biermasz *et al.* (14) observed reduced sleep efficiency, less rapid eye movement sleep, more N1 sleep, and more awakenings in the absence of excessive apnea or periodic limb movements in patients previously treated for nonfunctioning pituitary macroadenomas compared with age-, gender-, and BMI-matched controls. Actigraphy revealed a longer sleep duration and profound disturbances in diurnal movement patterns, with more awakenings at night and less activity during the day. Patients scored higher on fatigue and reported impaired QoL than healthy controls.

Regarding depressive symptoms in pituitary patients, the data seems to be relatively clear. Sievers *et al.* (15) and Tiemensma *et al.* (16) showed that acromegaly is associated with an increased prevalence and a specific pattern of affective disorders. Also for Cushing's disease, many studies have stressed that depression and anxiety-related personality disorders are common comorbidities in these patients (17, 18, 19, 20, 21). Patients with prolactinomas seem to experience increased neuroticism, high fear of uncertainty, and also increased fatigability and asthenia (22), but further studies are lacking. For patients with NFPAs, such data are still missing. Weitzner *et al.* (23) assumed that emotional problems (e.g., depression, anxiety) of patients with pituitary adenoma could be a result of long-term effects that the pituitary tumor itself, treatment, and/or hormonal changes have on the hypothalamic–pituitary–end organ axis; however, they presented four cases in which treatment for depression showed only little response, but treatment for apathy syndrome improved patients' conditions.

In summary, while impaired QoL has been a consistent finding in patients with pituitary adenomas, treatment of the underlying disorders has only partial effects on QoL in these patients. Possible determinants of QoL are depressive mood and reduced sleep quality, with the former already demonstrated in some but not all patient groups with pituitary adenomas, and the latter rather neglected so far. The aim of this study was, therefore, to explore QoL, depression, and sleep quality in all pituitary patient groups and to explore the association of sleep quality and depression with QoL in patients with pituitary adenomas.

Subjects and methods

Subjects

This study was a case–control study. Patients diagnosed with acromegaly ($n=62$), Cushing's disease ($n=58$),

prolactinomas ($n=74$), and NFPAs ($n=53$) were recruited from the Endocrine Outpatient Unit of the Max Planck Institute of Psychiatry and the Department of Internal Medicine, Ludwig-Maximilians-University, in Munich between 2007 and 2010 (response rate 56%, for further informations see e.g., Sievers *et al*. (15)). Reasons for nonparticipation were relocation and distance to study centers or unwillingness to spend time and effort on examinations. Exclusion criteria were the inability or unwillingness to perform the psychopathological assessments (i.e., insufficient language skills or diagnosed dementia).

The control subjects were selected from the 2007 follow-up assessment of the Diabetes Cardiovascular Risk Evaluation: Targets and Essential Data for Commitment of Treatment (DETECT) study (24). DETECT is a large multistage prospective-longitudinal study. The baseline study consisted of a nationwide representative sample of doctors with primary care functions (medical practitioners, general practitioners, and general internists), and included a total of 55 518 unselected consecutive patients in 3188 primary care offices in Germany. In the DETECT study, a representative sample of 7519 subjects was randomly chosen out of the baseline sample for additional laboratory tests and evaluated for a 5-year time period. For our control population, we matched one:max four controls selected from the follow-up assessment by age and gender to our patients and obtained hereby a group of 757 individually matched controls.

All subjects gave their written informed consent. The study was approved by the local ethic committee.

Diagnosis of pituitary adenomas, assessment of comorbidities, and biochemical variables and pituitary patient group

The clinical characteristics of the patients with pituitary adenomas were assessed via clinical interviews, physical examination, and laboratory analyses. Tumour characteristics were determined by magnetic resonance imaging including a specific sellar protocol including contrast medium. Visual field defects at the time of diagnosis were reported. In addition, history of treatment (surgery, radiotherapy, and medication), history of comorbidities including cardiovascular features, metabolic features, respiratory features, bone and joint features, malignancies and endocrine consequences such as thyroid goiter and pituitary deficiencies, past medical history, and actual symptoms were reported.

Somatic comorbidities were diagnosed according to standard diagnostic procedures. Therapies used followed the consensus treatment guidelines for the respective pituitary disease.

For acromegaly, the current biochemical disease control was evaluated based on the consensus criteria with i) GH below 1 μg/l during a glucose tolerance test over 2 h (if available) and ii) IGF1 within two S.D. of an age- and gender-adjusted normative range (25, 26). Serum concentrations of GH were measured using the automated advantage chemiluminescent assay system (Nichols Diagnostics Institute, Bad Vilbel, Germany), and IGF1 was measured by automated chemiluminescent assays (IMMULITE 2000) (27, 28).

Biochemical disease control of hypercortisolism in Cushing's disease was i) urinary free cortisol values greater than the normal range for the assay and ii) serum cortisol >1.8 g/dl (50 nmol/l) after 1 mg dexamethasone (1 mg DST), according to the Endocrine Society Clinical Practice Guideline 2008 (29).

Biochemical disease control in the prolactinoma patients was defined as PRL under the upper normal range of 25 ng/ml for women and 20 ng/ml for men with the commonly used assays for men (1 ng/ml is equivalent to 21.2 mIU/l WHO Standard Reference Number 84/500).

Evaluation of pituitary function comprised basal fasting measurements of IGF1, thyrotropin, free thyroxine, total triiodothyronine, luteinizing hormone, follicle-stimulating hormone, PRL, and testosterone (in men) or estradiol (in women) in all patients, as well as stimulation tests such as a short adrenocorticotropin test, the GH-releasing hormone/arginine test or insulin–hypoglycemia test in the case of suspected pituitary deficiencies in the corticotroph or somatotroph axis.

All patients with secondary hypoadrenalism, hypothyroidism, hypogonadism, and hyposomatotropism were studied while on optimized replacement therapy (including hydrocortisone, thyroid hormone, transdermal gonadal steroids or i.m. testosterone, and GH therapy where appropriate).

Assessment of depression

Depression was categorized as 'no depression', 'subclinical depression', and 'clinical depression' according to the Beck Depressions Inventory (BDI) for patients (BDI: 0–9, 10–18, >18), and the Depression Screening Questionnaire (DSQ) for control subjects (DSQ: 0–4, 5–7, >7) (30, 31). The psychometric properties of the DSQ are considered as satisfying (32, 33, 34).

Assessment of QoL

QoL was measured by the generic preference-based EQ-5D (35) which quantifies health-related QoL in five different dimensions (mobility, self-care, usual activities, pain and discomfort, anxiety and depression). Patients and controls rated their health state with the use of the EQ-5D descriptive system. Each dimension has three levels (level 1: no health problems, level 2: moderate health problems, and level 3: extreme health problems). A unique health state is assigned for each subject ranging from '11 111' (perfect health) and '33 333' (worst possible state), resulting in a total of 243 health states. German reference values were used for calculating the QoL index by the time trade-off (TTO) and VAS method (31). In general, in the TTO health state valuation method, subjects are asked how much of their life expectancy they would be willing to trade for a shorter life in full health (36, 37, 38).

Assessment of sleep quality

Sleep quality was assessed with the Pittsburgh Sleep Quality Index (PSQI) (39), an established international measure of sleep quality. The PSQI consists of 19 items, relates to the last 1-month time interval, and generates an overall score and seven component scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. In this study, we considered subjective sleep latency, sleep duration, sleep efficiency, and the global score. The global score has a range of 0–21 points with a higher number of points indicating poorer sleep quality. The controls answered a shorter version of the PSQI where three items had been omitted. To accommodate for this, we explored the relationship between the full and the abbreviated scale in a large independent sample of psychiatric–neurological patients ($n=82$), healthy subjects ($n=160$), and persons with sleeping disorders ($n=144$). Consistent across groups, the abbreviated score was systematically related by a factor of 1.134 to the full score and we therefore weighted the control subjects' PSQI global score by this factor.

Statistical analyses

All descriptive statistics are given as simple statistics for the patient groups and as weighted statistics for the control group with weighting factor being 1/m and m being the number of matched control subjects per single patient.

To compare BMI, frequency of comorbidities, depression, QoL, and sleep between all patient and controls and within each subgroup of patients and controls, general linear and generalized, logistic mixed models were used with a random intercept for each individual patient–control group.

In addition, we tested whether differences between patients and controls in depression, QoL, and sleep parameters were different for: i) patient groups (acromegaly, Cushing's disease, prolactinomas, NFPAs); ii) age groups (up to 45, 46–55, 56–65, >66 years); iii) men vs women; and iv) patients that are considered as biochemically controlled vs those that were not (only in three groups: acromegaly, Cushing's disease, prolactinomas). These were tested with a group (patients vs controls)× subgroup interaction effect in linear (sleep, QoL) and proportional odds (depression categories) mixed models, which tests the hypothesis that patient–control differences are larger or smaller in specific patient groups, age groups, or in men and women. All analyses were controlled for between group differences in BMI and comorbidities.

To explore the role of depression and sleep quality with regard to between-group differences in QoL, we compared a model with only group differences (model 1) with one where we controlled additionally for differences in sleep quality (model 2), depression (model 3), or both (model 4). The best linear unbiased predictions and approximate standard errors were derived from these mixed effects models for comparison.

All data analysis was undertaken with R 2.15.1 (40) and the nlme (41), the lme4 (42) and ordinal (43) packages in R.

Results

The characteristics of patient and control groups are given in Tables 1 and 2. Patients were aged 53.25±12.16 years, and had a mean BMI of 27.11±6.08 kg/m^2. The prevalence of cardiovascular disease for patients was 20%, of arterial hypertension 44%, of diabetes mellitus 15%, and of pulmonary disease 9%.

Patients differed from their matched control subjects in the following characteristics: BMI, hypertension, diabetes mellitus, and cardiovascular disease. Therefore, all effects were estimated controlling for between group differences in these variables.

Quality of life

Overall, patients with pituitary adenomas reported lower QoL as evaluated with the VAS and TTO index

Table 1 Description of patients and controls.

	Groups		Subgroups								Effects	
			Acromegaly		Cushing's disease		Prolactinomas		Nonfunctioning pituitary adenomas		Group	Group × subgroup
	Patients ($n=247$)	Controls ($n=757$)	Patients ($n=62$)	Controls ($n=187$)	Patients ($n=58$)	Controls ($n=172$)	Patients ($n=74$)	Controls ($n=224$)	Patients ($n=53$)	Controls ($n=174$)	Test statistic, P	Test statistic, P
Sex (male/female, n (%))	91/156 (37/63)	280/477 (37/63)[a]	29/33 (47/53)	88/91 (47/53)[a]	11/47 (19/81)	34/138 (19/81)[a]	16/58 (22/78)	48/176 (22/78)[a]	35/18 (66/34)	110/64 (66/34)[a]		
Age (years, mean ± s.d.)	53.25 ± 12.16	53.25 ± 12.15[a]	54.21 ± 11.08	54.21 ± 11.03[a]	49.88 ± 11.77	49.88 ± 11.71[a]	50.31 ± 12.91	50.31 ± 12.85[a]	59.96 ± 9.90	59.96 ± 9.84[a]		
BMI (kg/m^2, mean ± s.d.)	27.11 ± 6.08	27.17 ± 5.66[a]	**29.24 ± 5.50**[b]	27.25 ± 5.74[a]	25.66 ± 5.27	27.00 ± 5.65[a]	25.33 ± 6.93	26.58 ± 6.12[a]	28.68 ± 5.20	28.08 ± 4.80[a]	$F=0.061$ $P=0.805$	$F=4.170$ **$P=0.006$**
Duration of disease (years, mean ± s.d.)	12.27 ± 8.66		13.19 ± 9.75		11.17 ± 9.95		11.82 ± 7.14		13.07 ± 7.62			
Primary adenoma type												
Micro (%)	24.4		10.1		26.6		48.1		6.9			
Macro (%)	52.2		66.7		14.4		48.1		82.8			
Unknown size (%)	23.3		23.2		59.4		3.8		10.3			
Treatment												
Surgery (%)	66.7		91.3		85.9		13.9		87.9			
Radiotherapy (%)	15.9		27.5		14.1		1.3		24.1			
Medical treatment (%)	53.0		73.9		26.6		94.9		93.1			
Biochemical disease control (%)[c]	65.0		62.9		63.8		67.6					

[a]Frequencies, proportions, means, and s.d. are weighted summaries, accounting for differences in the number of matched controls per patient.
[b]Differs from respective control group with $P<0.05$.
[c]According to laboratory values.

Table 2 Description of comorbidities.

	Groups		Subgroups								Effects	
			Acromegaly		Cushing's disease		Prolactinomas		Nonfunctioning pituitary adenomas		Group	Group × subgroup
	Patients ($n=247$)	Controls ($n=757$)	Patients ($n=62$)	Controls ($n=187$)	Patients ($n=58$)	Controls ($n=172$)	Patients ($n=74$)	Controls ($n=224$)	Patients ($n=53$)	Controls ($n=174$)	Test statistic, P	Test statistic, P
Comorbidities												
Cardiovascular disease (%)	20	15[a]	**35**[b]	16[a]	19	17[a]	16	12[a]	9	17[a]	$z=1.749$ $P=0.080$	$\chi^2=14.79$ **$P=0.025$**
Hypertension (%)	**44**[b]	54[a]	56	53[a]	60	52[a]	**22**[b]	54[a]	43	59[a]	$z=-3.189$ **$P=0.001$**	$\chi^2=27.16$ **$P<0.001$**
Diabetes mellitus (%)	15	19[a]	27	23[a]	19	17[a]	**4**[b]	22[a]	11.32	15.09[a]	$z=-1.301$ $P=0.193$	$\chi^2=18.01$ **$P=0.006$**
Pulmonary disease (%)	9	11[a]	8	8[a]	10	16[a]	12	9[a]	2	11[a]	$z=-0.935$ $P=0.350$	$\chi^2=7.62$ $P=0.266$

[a]Frequencies, proportions, means, and s.d. are weighted summaries, accounting for differences in the number of matched controls per patient.
[b]Differs from respective control group with $P<0.05$.

Table 3 Differences in depression, quality of life, and sleep between patients and controls.

	Groups		Effects	
			Group	Group×subgroup
	Patients ($n=247$)	Controls ($n=757$)	Test statistic, P	Test statistic, P
Depression			$\chi^2=16.261$ **$P<0.0001$**	$\chi^2=9.581$ $P=0.434$
No depression (%)	58.70[a]	74.07[b]		
Subclinical (%)	25.51[a]	13.70[b]		
Clinical (%)	15.79[a]	12.22[b]		
Quality of life				
VAS$^{\uparrow}$ (mean±s.d.)	**0.73±0.19**[a]	0.79±0.18[b]	$F=26.109$ **$P<0.0001$**	$F=3.777$ **$P=0.0104$**
TTO$^{\uparrow}$ (mean±s.d.)	**0.83±0.22**[a]	0.88±0.18[b]	$F=10.616$ **$P=0.0012$**	$F=2.982$ **$P=0.0307$**
Sleep parameters				
Sleep latency (min, mean)[c]	24.41	20.09	$F=2.311$ $P=0.1288$	$F=1.721$ $P=0.1613$
Sleep duration (decimal hours, mean±s.d.)	6.71±1.25	6.61±1.19[c]	$F=1.486$ $P=0.2232$	$F=0.379$ $P=0.7680$
Sleep efficiency (%, mean±s.d.)	84.29±14.11	83.74±14.20[c]	$F=0.011$ $P=0.9156$	$F=0.603$ $P=0.6131$
PSQI-score$^{\downarrow}$ (mean±s.d.)	**6.75±4.17**[a]	5.66±4.31[a]	$F=14.667$ **$P=0.0001$**	$F=0.900$ $P=0.4407$

VAS, quantified using the VAS method; TTO, quantified using the time trade-off (TTO) method; PSQI, Pittsburgh Sleep Quality Index. $^{\uparrow}$=higher values equal better quality of life, $^{\downarrow}$=lower values equal better sleep quality.
[a]Differs from respective control group with $P<0.05$.
[b]Frequencies, proportions, means, and s.d. are weighted summaries, accounting for differences in the number of matched controls per patient.
[c]Was log transformed for all analyses.

(Table 3) respectively. We also observed a significant group×subgroup interaction effect, with a larger reduction in QoL – measured by the VAS – in patients with Cushing's disease compared with all other groups (Table 3). Gender, age, or the biochemical disease control of the patients had no influence on patient–control differences in QoL.

Sleep quality

For this study, we compared subjective sleep duration, sleep onset latency, sleep efficiency, and the PSQI global score between patients and controls (Table 3). There was no difference between patient and controls in sleep duration, sleep onset latency, or subjective sleep efficiency and neither age, gender, nor treatment status had an influence on patient–control differences in these variables.

In contrast, the PSQI score was significantly increased in patients with pituitary adenomas. This patient–control difference did not depend on the specific patient group, age, gender, or the biochemical disease control.

Depression

Overall, patients with pituitary adenoma had average BDI scores of 9.87±9.16. There was a significant difference between patient groups ($F=3.589$, $P=0.014$). BDI scores were significantly higher for patients with Cushing's disease (13.21±9.94) than for all other patient groups (acromegaly 8.76±8.40, prolactinomas 9.32±9.80, NFPAs 8.30±7.34). This difference, however, was no longer statistically significant when controlling for differences in age and gender between patient groups ($F=2.128$, $P=0.097$).

For both patients and controls, depression scores had been classified as no depression, subclinical depression, and depression (see 'Materials and methods' section). Proportional odds mixed models showed that the incidence of both subclinical and clinical depression was higher in patients with pituitary adenomas (Table 3). This difference was not dependent on the specific patient group, the age, or the biochemical disease control of the patient. Gender, however, had a significant influence on the patient–control differences in depression ($\chi^2=16.746$, $P<0.001$). Although in both patient and control groups, more females showed depressive symptoms, the difference between patient and controls was even higher for females (Fig. 1).

The role of depression for QoL and sleep quality

As patients differed from controls in QoL, sleep quality, and depression, we sought to determine to what extent

depression and sleep quality accounted for the differences in QoL. To that end, we compared predictions for patient–control differences derived from a model with only the group effect (model 1), with predictions when controlling for differences in sleep (PSQI global score, model 2), depression (model 3), or both (model 4). The results are illustrated in Fig. 2. The significant difference between patients and controls in the QoL (VAS scores: $F=26.109$, $P<0.001$) remained significant when controlling for sleep quality ($F=13.829$, $P<0.001$), depression ($F=13.448$, $P<0.001$), or both ($F=10.284$, $P=0.001$). The magnitude of the expected difference between patient and controls, however, was considerably decreased by 34% (sleep quality), 39% (depression), and 48% (sleep quality and depression).

This effect was even more pronounced when considering the TTO. While in the basic model, there were significant differences between patients and controls ($F=10.616$, $P=0.001$), there was only a trend when controlling for sleep quality ($F=3.577$, $P=0.059$) or depression ($F=2.970$, $P=0.085$). When controlling for both sleep and depression, a difference between patients and controls was no longer observable ($F=1.690$, $P=0.194$). Controlling for differences in sleep quality reduced the observed patient–control differences by 46%, control for depression reduced the difference by 53%, and accounting for both variables decreased the effect by 65% (Fig. 2, right panel).

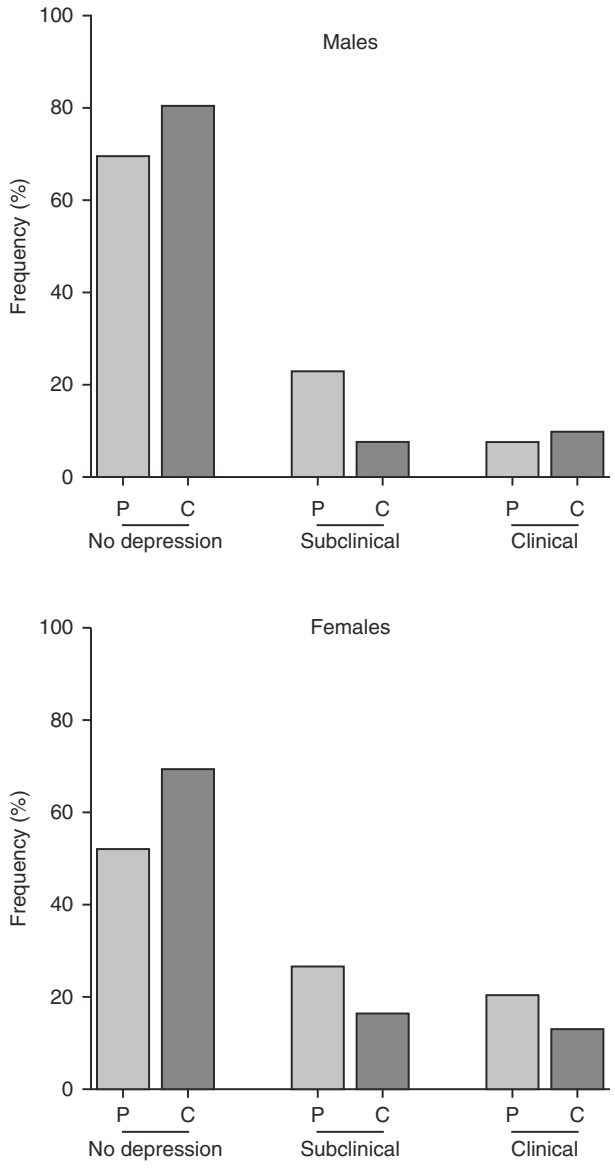


Figure 1

Frequency of depressive categories in patients with pituitary adenomas (P) and matched controls (C). Gender had a significant influence on the patient–control differences in depression ($\chi^2=16.746$, $P<0.001$). Although in both patient and control groups, more females showed depressive symptoms, the difference between patient and controls was even higher for females.

Discussion

This large case–control study including 247 patients and 757 controls aimed at investigating the role of depression and sleep on QoL in patients with acromegaly, Cushing's disease, prolactinomas, and NFPAs. This study provides the first and most comprehensive results comparing patients with different pituitary adenomas.

The main findings of our study are as follows: patients with pituitary adenomas reported decreased QoL as well as decreased subjective sleep quality compared with healthy controls; there was a larger reduction in QoL in patients with Cushing's disease compared with all other patient groups; the incidence of both subclinical and clinical depression was higher in patients with pituitary adenomas; and a substantial proportion of the reduced QoL (48% respectively 65%) in patients with pituitary adenomas is due to the incidence of depression and reduced sleep quality.

Patients with pituitary adenomas reported decreased QoL and sleep compared with their matched controls. These findings are in accordance with previous results about QoL in patients with pituitary adenomas (1) as well as with results about the subjective sleep quality of individual patient groups, e.g. of acromegaly (10), NFPAs (14), or craniopharyngeomas (44).

In addition, patients with Cushing's disease showed a larger reduction in QoL compared with all other patient groups. Moreover, we could not find any significant differences in QoL between patients and controls in subgroups based on different sex and age, as well as in the subgroups of biochemically cured patients and those who were not cured. The result of decreased QoL despite long-term biochemical cure is in accordance with previous findings (1, 2, 6, 7, 45, 46).

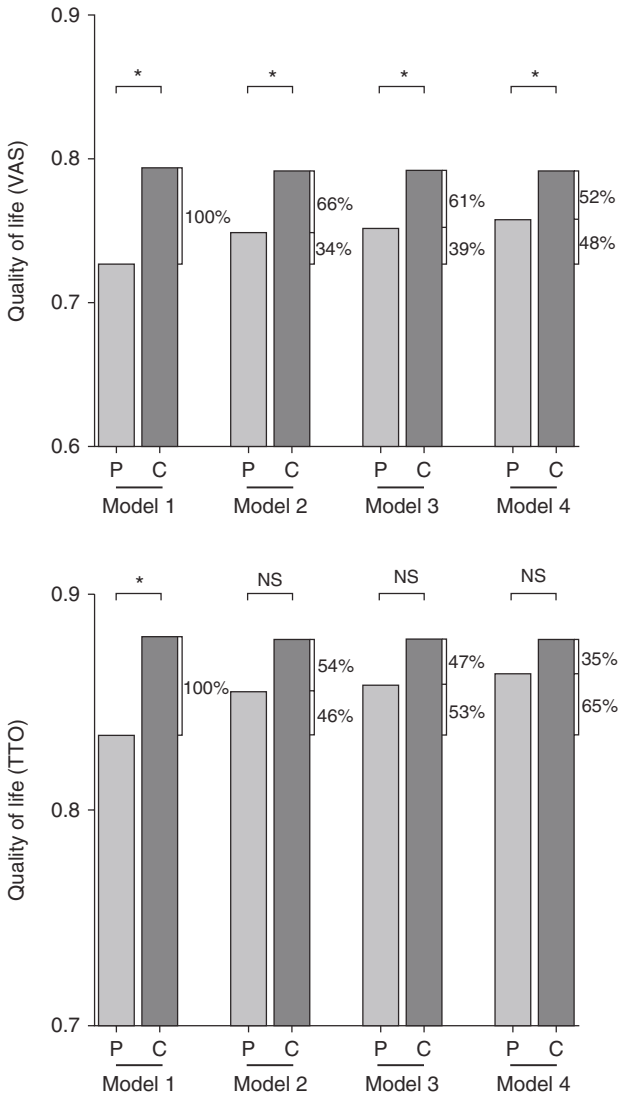


Figure 2

Effect of controlling for differences in sleep quality and depression on patient (P)–control (C) differences in quality of life measures. Left panel, VAS; right panel, TTO. AS and TTO are methods to calculate QoL assessed with the EQ-5D whereas the higher the score the better the QoL. All models are controlled for differences in BMI, hypertension, cardiovascular disease, and diabetes between patients and controls. Interval for approximate standard errors: VAS = (0.143–0.175) and TTO = (0.162–0.188). NS, no significant differences between patients and controls; *patients differ from control group with $P < 0.05$.

Furthermore, the results of our study suggest that patients with pituitary adenomas differ from control subjects in depression: while only 25% of primary care–control subjects, nearly 41% of patients showed subclinical respectively clinically relevant depression. Patients with Cushing's disease showed also the highest rates of depression compared with other patient groups. So far, psychiatric aspects of Cushing's disease have been the best described in the recent literature (17, 18, 19, 20). However, the higher incidence of depression for patients with Cushing's disease in our study is partly explained by the fact that there are predominantly females in this group. This may explain why a previous study (1) had found no disease-specific differences in the subscales of the Hospital Anxiety and Depression Scale comparing patients with acromegaly, Cushing's disease, prolactinomas, and NFPAs. Gender had a significant influence on the patient–control differences in depression. Although in both patient and control groups, more females showed depressive symptoms, the difference between patient and controls was even higher for females. Taken into account that higher rates of affective disorders are more frequent in females in general, these results are not surprising. Nevertheless, it suggests that women may be especially vulnerable to the consequences of their disease.

Finally, we could show that a substantial proportion of the reduced QoL is due to the incidence of depression and reduced sleep quality. Up to now, there has been only evidence for Cushing's disease that depression leads to a reduced QoL (47). Because both depression and sleep quality can be treated, this offers complementary approaches for the improvement of patients' conditions in contrast to previous recommendations (23). Whether this will improve QoL in these patients has to be investigated in further studies.

Limitations

This study has several limitations which we have to take into account when interpreting the results. The control group consisted of primary care patients and not healthy controls (for further information (48)). Therefore we cannot exclude that control subjects showed decreased QoL and impaired sleep quality or increased rates of depression for other reasons, too. Hence, we might have underestimated the

differences between patients and controls in depression, QoL, and sleep, which might be even larger compared with healthy subjects. Furthermore, we did not control for differences in drug use/intake, especially in antidepressants and sleep-inducing drugs, respectively, and differences due to receiving other treatments for depression, e.g. psychotherapy. On the other hand, if there had been differences, misclassification of patients would have resulted in lower rates of depression and respectively better sleep quality. Moreover, we have to consider that pituitary patients and primary care controls had different backgrounds: controls were recruited from a nationwide primary care population, while pituitary patients were recruited from a referral area for endocrine patients. However, as our main outcomes are depression/sleep/QoL and both groups are patients with somatic diseases, there should not be a preferential selection of patients with psychiatric symptoms in one or the other cohort. Only patients with acromegaly were evaluated for obstructive sleep apnea by asking them for previous screenings. Since that information could not be classified as objective and reliable data, we did not include them in the analyses. Furthermore, we cannot exclude that reduced QoL, impaired sleep quality, and depression in patients are partly due to disease-related problems. But since duration of disease averages about 12 years, we did not measure only the acute reaction after the diagnosis. However, the reasons for impaired sleep quality, depression, and as consequence for a reduced QoL should play a certain role in designing disease-specific interventions for these patients. More importantly, the use of two different measures of depression (BDI for patients and DSQ for controls) is not ideal. However, as we felt that a pituitary-independent comparison group would be helpful to study the burden of symptoms in relationship with other primary care patients, we decided to design the study as presented with the compromise that we could only use the categorized variable 'depression'. As we did not compare raw values of different instruments, but frequencies of depression categorized as 'no depression', 'subclinical depression', and 'clinical depression', we believe that comparability should be high. Finally, this study is a cross-sectional case–control study but not a longitudinal survey. No causal conclusions can be drawn from the data, but we contribute to the important question which factors due to a reduced QoL in patients with pituitary adenomas.

Conclusion

In conclusion, our findings of reduced QoL and sleep as well as increased rates of depression in patients with pituitary adenomas may have implications for the long-term management of these patients. The knowledge that a substantial proportion of the reduced QoL is due to the incidence of depression and reduced sleep quality emphasizes the need for a diagnostic work-up including these entities with the ultimate goal to improve QoL in these patients.

Declaration of interest

C Sievers received lecture fees and independent research grants from Pfizer Pharma GmbH Berlin and Novartis Pharma GmbH. C Dimopoulou received lecture fees from Pfizer Pharma GmbH Berlin and Novartis Pharma GmbH. H-U Wittchen has been on advisory boards of Servier, Pfizer, and Lundbeck, received via his university grant support by Novartis, Lundbeck, and Pfizer and travel compensation for scientific meetings from Servier, Pfizer, Lundbeck, and Novartis. S M Leistner, J Klotsche, A P Athanasoulia, J Roemmler-Zehrer, L Pieper, J Schopohl, G K Stalla, S Fulda have nothing to declare.

Funding

This study was supported by an unrestricted grant from Pfizer GmbH, Berlin, Germany. DETECT (Diabetes Cardiovascular Risk-Evaluation: Targets and Essential Data for Commitment of Treatment) is a cross-sectional and prospective-longitudinal, nationwide clinical epidemiological study. DETECT is supported by an unrestricted educational grant of Pfizer GmbH, Berlin, Germany. Members of the DETECT-Study group include: Principal investigator: Prof. Dr H-U Wittchen; Staff members: Dr L Pieper, Dr J Klotsche, Dr T Eichler, Dr H Glaesmer, E Katze. Steering Committee: Prof. Dr H Lehnert (Lübeck), Prof. Dr G K Stalla (München), Prof. Dr A M Zeiher (Frankfurt); Advisory Board: Prof. Dr W März (Heidelberg/Graz), Prof. Dr S Silber (München), Prof. Dr U Koch (Hamburg), Prof. Dr D Pittrow (München/Dresden), Prof. Dr M Wehling (Mannheim), Dr D Leistner (Frankfurt), Dr H J Schneider (München), PD Dr C Sievers (München).

References

1 van der Klaauw AA, Kars M, Biermasz NR, Roelfsema F, Dekkers OM, Corssmit EP, van Aken MO, Havekes B, Pereira AM, Pijl H *et al*. Disease-specific impairments in quality of life during long-term follow-up of patients with different pituitary adenomas. *Clinical Endocrinology* 2008 **69** 775–784. (doi:10.1111/j.1365-2265.2008.03288.x)

2 Biermasz NR, van Thiel SW, Pereira AM, Hoftijzer HC, van Hemert AM, Smit JW, Romijn JA & Roelfsema F. Decreased quality of life in patients with acromegaly despite long-term cure of growth hormone excess. *Journal of Clinical Endocrinology and Metabolism* 2004 **89** 5369–5376. (doi:10.1210/jc.2004-0669)

3 Webb SM. Quality of life in acromegaly. *Neuroendocrinology* 2006 **83** 224–229. (doi:10.1159/000095532)

4 Johnson MD, Woodburn CJ & Vance ML. Quality of life in patients with a pituitary adenoma. *Pituitary* 2003 **6** 81–87. (doi:10.1023/B:PITU.0000004798.27230.ed)

5 Paisley AN, Rowles SV, Roberts ME, Webb SM, Prieto BL, Shalet SM & Trainer PJ. Treatment of acromegaly improves quality of life, measured by AcroQol. *Clinical Endocrinology* 2007 **67** 358–362. (doi:10.1111/j.1365-2265.2007.02891.x)

6 Heald AH, Ghosh S, Bray S, Gibson C, Anderson SG, Buckler H & Fowler HL. Long-term negative impact on quality of life in patients with

successfully treated Cushing's disease. *Clinical Endocrinology* 2004 **61** 458–465. (doi:10.1111/j.1365-2265.2004.02118.x)
7 van Aken MO, Pereira AM, Biermasz NR, van Thiel SW, Hoftijzer HC, Smit JW, Roelfsema F, Lamberts SW & Romijn JA. Quality of life in patients after long-term biochemical cure of Cushing's disease. *Journal of Clinical Endocrinology and Metabolism* 2005 **90** 3279–3286. (doi:10.1210/jc.2004-1375)
8 Kars M, van der Klaauw AA, Onstein CS, Pereira AM & Romijn JA. Quality of life is decreased in female patients treated for microprolactinoma. *European Journal of Endocrinology* 2007 **157** 133–139. (doi:10.1530/EJE-07-0259)
9 Naliato E, Violante AH, Caldas D, Filho AL, Loureiro CR, Fontes R, Schrank Y, de Souza RG, Vaisman M, Guerra E *et al*. Quality of life in women with microprolactinoma treated with dopamine agonists. *Pituitary* 2008 **11** 247–254. (doi:10.1007/s11102-008-0091-9)
10 Copinschi G, Nedeltcheva A, Leproult R, Morselli LL, Spiegel K, Martino E, Legros JJ, Weiss RE, Mockel J & Van Cauter E. Sleep disturbances, daytime sleepiness, and quality of life in adults with growth hormone deficiency. *Journal of Clinical Endocrinology and Metabolism* 2010 **95** 2195–2202. (doi:10.1210/jc.2009-2080)
11 van der Klaauw AA, Pereira AM, van Kralingen KW, Rabe KF & Romijn JA. Somatostatin analog treatment is associated with an increased sleep latency in patients with long-term biochemical remission of acromegaly. *Growth Hormone & IGF Research* 2008 **18** 446–453. (doi:10.1016/j.ghir.2008.04.001)
12 Frieboes RM, Murck H, Stalla GK, Antonijevic IA & Steiger A. Enhanced slow wave sleep in patients with prolactinoma. *Journal of Clinical Endocrinology and Metabolism* 1998 **83** 2706–2710. (doi:10.1210/jcem.83.8.5016)
13 van der Klaauw AA, Biermasz NR, Pereira AM, van Kralingen KW, Dekkers OM, Rabe KF, Smit JW & Romijn JA. Patients cured from craniopharyngioma or nonfunctioning pituitary macroadenoma (NFMA) suffer similarly from increased daytime somnolence despite normal sleep patterns compared to healthy controls. *Clinical Endocrinology* 2008 **69** 769–774. (doi:10.1111/j.1365-2265.2008.03284.x)
14 Biermasz NR, Joustra SD, Donga E, Pereira AM, van Duinen N, van Dijk M, van der Klaauw AA, Corssmit EP, Lammers GJ, van Kralingen KW *et al*. Patients previously treated for nonfunctioning pituitary macroadenomas have disturbed sleep characteristics, circadian movement rhythm, and subjective sleep quality. *Journal of Clinical Endocrinology and Metabolism* 2011 **96** 1524–1532. (doi:10.1210/jc.2010-2742)
15 Sievers C, Dimopoulou C, Pfister H, Lieb R, Steffin B, Roemmler J, Schopohl J, Mueller M, Schneider HJ, Ising M *et al*. Prevalence of mental disorders in acromegaly: a cross-sectional study in 81 acromegalic patients. *Clinical Endocrinology* 2009 **71** 691–701. (doi:10.1111/j.1365-2265.2009.03555.x)
16 Tiemensma J, Biermasz NR, van der Mast RC, Wassenaar MJ, Middelkoop HA, Pereira AM & Romijn JA. Increased psychopathology and maladaptive personality traits, but normal cognitive functioning, in patients after long-term cure of acromegaly. *Journal of Clinical Endocrinology and Metabolism* 2010 **95** E392–E402. (doi:10.1210/jc.2010-1253)
17 Kelly WF. Psychiatric aspects of Cushing's syndrome. *QJM: Monthly Journal of the Association of Physicians* 1996 **89** 543–551. (doi:10.1093/qjmed/89.7.543)
18 Sonino N, Fallo F & Fava GA. Psychosomatic aspects of Cushing's syndrome. *Reviews in Endocrine & Metabolic Disorders* 2010 **11** 95–104. (doi:10.1007/s11154-009-9123-7)
19 Tiemensma J, Biermasz NR, Middelkoop HA, van der Mast RC, Romijn JA & Pereira AM. Increased prevalence of psychopathology and maladaptive personality traits after long-term cure of Cushing's disease. *Journal of Clinical Endocrinology and Metabolism* 2010 **95** E129–E141. (doi:10.1210/jc.2010-0512)
20 Pereira AM, Tiemensma J & Romijn JA. Neuropsychiatric disorders in Cushing's syndrome. *Neuroendocrinology* 2010 **92** 65–70. (doi:10.1159/000314317)
21 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** 139–145. (doi:10.1159/000338408)
22 Athanasoulia AP, Ising M, Pfister H, Mantzoros CS, Stalla GK & Sievers C. Distinct dopaminergic personality patterns in patients with prolactinomas: a comparison with nonfunctioning pituitary adenoma patients and age- and gender-matched controls. *Neuroendocrinology* 2012 **96** 204–211. (doi:10.1159/000335996)
23 Weitzner MA, Kanfer S & Booth-Jones M. Apathy and pituitary disease: it has nothing to do with depression. *Journal of Neuropsychiatry and Clinical Neurosciences* 2005 **17** 159–166. (doi:10.1176/jnp.17.2.159)
24 Wittchen HU, Glaesmer H, Marz W, Stalla G, Lehnert H, Zeiher AM, Silber S, Koch U, Bohler S, Pittrow D *et al*. Cardiovascular risk factors in primary care: methods and baseline prevalence rates – the DETECT program. *Current Medical Research and Opinion* 2005 **21** 619–630. (doi:10.1185/030079905X38187)
25 Giustina A, Barkan A, Casanueva FF, Cavagnini F, Frohman L, Ho K, Veldhuis J, Wass J, Von Werder K & Melmed S. Criteria for cure of acromegaly: a consensus statement. *Journal of Clinical Endocrinology and Metabolism* 2000 **85** 526–529.
26 Giustina A, Chanson P, Bronstein MD, Klibanski A, Lamberts S, Casanueva FF, Trainer P, Ghigo E, Ho K & Melmed S. A consensus on criteria for cure of acromegaly. *Journal of Clinical Endocrinology and Metabolism* 2010 **95** 3141–3148. (doi:10.1210/jc.2009-2670)
27 Melmed S, Casanueva F, Cavagnini F, Chanson P, Frohman LA, Gaillard R, Ghigo E, Ho K, Jaquet P, Kleinberg D *et al*. Consensus statement: medical management of acromegaly. *European Journal of Endocrinology* 2005 **153** 737–740. (doi:10.1530/eje.1.02036)
28 Melmed S. Medical progress: acromegaly. *New England Journal of Medicine* 2006 **355** 2558–2573. (doi:10.1056/NEJMra062453)
29 Nieman LK, Biller BM, Findling JW, Newell-Price J, Savage MO, Stewart PM & Montori VM. The diagnosis of Cushing's syndrome: an Endocrine Society Clinical Practice Guideline. *Journal of Clinical Endocrinology and Metabolism* 2008 **93** 1526–1540. (doi:10.1210/jc.2008-0125)
30 Hautzinger M, Bailer M, Worall H & Keller F. *Beck-Depressions-Inventar – Testhandbuch*, Bern: Verlag Hans Huber, 1994.
31 Pieper L, Schulz H, Klotsche J, Eichler T & Wittchen HU. Depression as a comorbid disorder in primary care. *Bundesgesundheitsblatt, Gesundheitsforschung, Gesundheitsschutz* 2008 **51** 411–421. (doi:10.1007/s00103-008-0509-6)
32 Höfler M & Wittchen H-U. Why do primary care doctors diagnose depression when diagnostic criteria are not met? *International Journal of Methods in Psychiatric Research* 2000 **9** 110–120.
33 Wittchen HU, Hofler M & Meister W. Prevalence and recognition of depressive syndromes in German primary care settings: poorly recognized and treated? *International Clinical Psychopharmacology* 2001 **16** 121–135. (doi:10.1097/00004850-200105000-00001)
34 Wittchen HU, Kessler RC, Beesdo K, Krause P, Hofler M & Hoyer J. Generalized anxiety and depression in primary care: Prevalence, recognition, and management. *Journal of Clinical Psychiatry* 2002 **63** 24–34.
35 Schulenburg JM, Greiner W *et al*. Die deutsche Version des EuroQol-Fragebogens. *Zeitschrift für Angewandte Ichthyologie* 1998 3–20.
36 Torrance GW, Thomas WH & Sackett DL. A utility maximization model for Evaluation of Health Care Programs. *Health Services Research* 1972 **7** 118–133.
37 Buckingham K & Devlin N. A theoretical framework for TTO valuations of health. *Health Economics* 2006 **15** 1149–1154. (doi:10.1002/hec.1122)
38 Bernert S, Fernandez A, Haro JM, Konig HH, Alonso J, Vilagut G, Sevilla-Dedieu C, de Graaf R, Matschinger H, Heider D *et al*.

Comparison of different valuation methods for population health status measured by the EQ-5D in Three European Countries. *Value in Health* 2009 **12** 750–758. (doi:10.1111/j.1524-4733.2009.00509.x)
39 Buysse DJ, Reynolds CF, Monk TH, Berman SR & Kupfer DJ. The Pittsburgh Sleep Quality Index – a new instrument for psychiatric practice and research. *Psychiatry Research* 1989 **28** 193–213. (doi:10.1016/0165-1781(89)90047-4)
40 R Development Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing, 2012.
41 Pinheiro J, Bates D, DebRoy S, Sarkar D & R Development Core Team. nlme: Linear and Nonlinear Mixed Effects Models. edn R package version 3.1-108, 2013.
42 Bates D, Maechler M, Bolker B & R Development Core Team. Linear mixed-effects models using S4 classes. edn R package version 0.999999-0, 2012.
43 Christensen RH. Ordinal: Regression Models for Ordinal Data. edn R package version 2012.09-11, 2012.
44 Pickering L, Jennum P, Gammeltoft S, Poulsgaard L, Feldt-Rasmussen U & Klose M. Sleep-wake and melatonin pattern in craniopharyngioma patients. *European Journal of Endocrinology* 2014 **170** 873–884. (doi:10.1530/EJE-13-1025)
45 Rowles SV, Prieto L, Badia X, Shalet SM, Webb SM & Trainer PJ. Quality of life (QOL) in patients with acromegaly is severely impaired: use of a novel measure of QOL: acromegaly quality of life questionnaire. *Journal of Clinical Endocrinology and Metabolism* 2005 **90** 3337–3341. (doi:10.1210/jc.2004-1565)
46 Kauppinen-Makelin R, Sane T, Sintonen H, Markkanen H, Valimaki MJ, Loyttyniemi E, Niskanen L, Reunanen A & Stenman UH. Quality of life in treated patients with acromegaly. *Journal of Clinical Endocrinology and Metabolism* 2006 **91** 3891–3896. (doi:10.1210/jc.2006-0676)
47 Badia X, Valassi E, Roset M & Webb SM. Disease-specific quality of life evaluation and its determinants in Cushing's syndrome: what have we learnt? *Pituitary* 2014 **17** 187–195. (doi:10.1007/s11102-013-0484-2)
48 Pittrow D, Pieper L, Klotsche J, & Wittchen. H-U. DETECT – Ergebnisse einer klinisch-epdemiologischen Querschnitts- und Verlaufsstudie mit 55000 Patienten in 3000 Hausarztpraxen, München – Jena: Urban & Fischer, 2007.

Received 3 November 2014
Revised version received 5 March 2015
Accepted 19 March 2015

6. VERÖFFENTLICHUNG II

Original Paper

Neuro
-endocrinology

Neuroendocrinology
DOI: 10.1159/000448519

Received: December 7, 2015
Accepted after revision: July 19, 2016
Published online: July 25, 2016

Body Image Perception in Acromegaly Is Not Associated with Objective Acromegalic Changes but Depends on Depressive Symptoms

Christina Dimopoulou[a] Sarah M. Leistner[a] Marcus Ising[b] Harald J. Schneider[c] Jochen Schopohl[c] Sandra Rutz[c] Robert Kosilek[c] Richard Frohner[c] Gunter K. Stalla[a] Caroline Sievers[a]

Departments of [a]Clinical Neuroendocrinology and [b]Molecular Psychology, Max Planck Institute of Psychiatry, and [c]Medizinische Klinik und Poliklinik IV, Ludwig-Maximilians-University, Munich, Germany

Key Words
Body image · Acromegaly · Objective changes · Depression

Abstract
Objective: Diagnosis of acromegaly is delayed up to 10 years after disease onset despite obvious external/objective changes such as bone and soft tissue deformities. 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 workup. ***Design:*** Cross-sectional study. ***Methods:*** We investigated perceived body image by standardized questionnaires (FKB-20: Fragebogen zum Körperbild; FBeK: Fragebogen zur Beurteilung des eigenen Körpers) in 81 acromegalic patients and contrasted them to (a) a clinical control group of 60 patients with nonfunctioning pituitary adenomas (NFPA) who lack severe facial and physical alterations and (b) healthy controls. We further evaluated body image in relation to objective acromegalic changes as judged by medical experts and psychiatric pathology, e.g. depression and cognitive impairment. ***Results:*** Patients with acromegaly did not lack subjective perception of the disease state; they showed more negative body image, less vitality, more insecurity/paresthesia and more accentuation of the body compared to normal controls. NFPA patients differed from acromegalic patients only in the 'vital body dynamics' scale of the FKB-20, although they hardly exhibit any physical/bodily changes. Depression correlated with worse body image. No associations were found between body image and objective acromegalic changes as judged by medical experts, cognitive decline or treatment status. ***Conclusions:*** Negative body image in acromegalic patients is unrelated to their objective appearance and similar to those of NFPA patients without major bodily changes. Depression, but not cognitive decline or treatment status, contributes to negative body image.

Introduction

Acromegaly, a state of growth hormone (GH) excess, is a severe disfiguring disorder, characterized by numerous bone and soft-tissue deformities such acral growth, prognathism, macroglossia, soft tissue swelling, skin thickening and hypertrichosis [1]. Despite these objective physical alterations, in the vast majority of cases there is

KARGER

0028–3835/16/0000–0000$39.50/0

E-Mail karger@karger.com
www.karger.com/nen

Christina Dimopoulou, MD
Department of Clinical Neuroendocrinology
Max Planck Institute of Psychiatry, Kraepelinstrasse 2–10
DE–80804 Munich (Germany)
E-Mail chdimo@hotmail.com

a diagnostic delay of 6.6–10.2 years between onset of acromegalic symptoms and diagnosis, resulting in increased morbidity and mortality [1, 2]. Diagnostic delay in acromegaly is believed to be multifactorial including factors such as disease rarity and low detection rates by nonexperts, subtle disfiguring changes over time, different degrees of disease severity and emotional state of the patients themselves [3].

Previous studies have reported disturbed body image perception in patients with acromegaly [4, 5]. On the other hand, acromegalic patients have been found to suffer from an increased prevalence of psychopathology and affective disorders [6, 7]. Thus, it has been suggested that chronic GH/IGF-1 excess leads to irreversible changes in the central nervous system causing macroscopic brain structure changes and cognitive decline [8, 9]. To our knowledge, no association between disturbed body image perception and predisposing factors has been established so far.

The aim of this study was to investigate whether body image perception in patients with acromegaly differs from a clinical control group of patients with nonfunctioning pituitary adenomas (NFPA) who lack any physical/bodily changes. The underlying hypothesis was that acromegalic patients might lack subjective perception of the disease state despite marked objective changes. This inability to recognize objective physical changes might contribute to the delayed disease diagnosis. We further analyzed associations for negative body image with objective acromegalic changes as judged by medical experts and other potentially causal factors, e.g. psychiatric pathology such as depression, cognitive impairment and treatment status.

Subjects and Methods

Patients

We studied 81 patients with acromegaly (half of them treated at the Max Planck Institute of Psychiatry and half of them treated at the Klinikum der Universität, Innenstadt, Ludwig-Maximilians-University Munich) referred to our endocrinological specialty clinics between 1990 and 2012. As a clinical control group, we recruited 60 patients with NFPA. All subjects gave their written informed consent. The study was approved by the local ethical committee.

Assessment of Body Image

FKB-20 (Fragebogen zum Körperbild)

The German FKB-20 (Fragebogen zum Körperbild) questionnaire was developed and validated by Clement and Löwe in 1996 [10, 11] in order to gain assessable data for body image disturbances. The questionnaire comprises 20 items, which can be answered on a five-point scale (not accurate, barely accurate, partially accurate, widely accurate, fully accurate) and measures in a very economical way two independent dimensions of body image, 'negative body image' (NBI) and 'vital body dynamics' (VBD). NBI refers to a person's negative attitude towards their own body and, on the other hand, judges the feeling of consistency and well-being in their own body. VBD describes one's perception of personal vitality, deals with the energy and movement-related aspect of body image and describes to what extent strength, fitness and health are perceived by the patient. Low individual NBI scores reflect a good subjective body image, while low VBD scores indicate a negative perception of vitality. The FKB-20 was found to have good validity, with validity coefficients ranging from 0.56 to 0.65. The sensitivity of the questionnaire was 82–90%, the specificity 90–97% and the total error rate 8–10% [10, 11].

FBeK (Fragebogen zur Beurteilung des eigenen Körpers)

The questionnaire to assess the own body (Fragebogen zur Beurteilung des eigenen Körpers) is one of the most frequently used German questionnaires in the field of body experience [12–14]. It comprises 52 items and can be assessed according to the original three-scale solution (first scale: 'insecurity/concerns', 19 items; second scale: 'attraction/self-confidence', 13 items; third scale: 'accentuation of the body/sensitivity', 20 items) or according to the revised four-scale solution, in which 6 out of 52 items are not considered in the final evaluation (first scale: 'attraction/self-confidence', 15 items; second scale: 'accentuation of the body/sensitivity', 12 items; third scale: 'insecurity/concerns', 13 items, and fourth scale: 'bodily-sexual misfeelings', 6 items). We chose the original scale model (three-scale model), as there is stronger evidence for validity [14].

Assessment of Depression

Depression was categorized as 'no depression' (Beck Depression Inventory, BDI-II <10), 'mild-moderate depression' (10 < BDI-II < 18) and 'clinical depression' (BDI-II ≥18) according to the BDI-II for patients [15].

Assessment of Comorbidities, Biochemical Variables and Tumour Characteristics

Clinical characteristics of the study population were assessed via interview, physical examination and laboratory analyses. Tumour characteristics were determined by thin-section magnetic resonance imaging (2 mm) of the pituitary comprising dynamic sequences. Visual field defects were confirmed by Goldmann perimetry. Additionally, details on treatment history (surgery, radiotherapy and medication), history of comorbidities, past medical history and actual symptoms were collected from patients' charts. Patients were treated according to the consensus treatment guidelines for the respective pituitary disease [16, 17].

Biochemical control of acromegaly was defined as (a) GH below 1 μg/l during a glucose tolerance test over 2 h (if available), and (b) IGF-1 within two standard deviations of an age- and gender-adjusted normative range [18]. Evaluation of pituitary function comprised basal fasting measurements of IGF-1, TSH, free thyroxine (FT4), total triiodothyronine (T3), LH, FSH, prolactin and testosterone (in men) or oestradiol (in women) in all patients, as well as an insulin tolerance test in the case of suspected pituitary deficiencies in the corticotroph or somatotroph axis. All patients with secondary hypoadrenalism, hypothyroidism, hypogonadism and hyposomatotropism were studied while on optimized replacement therapy.

Table 1. Clinical characteristics of the study population

	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.

Assessment of Cognition

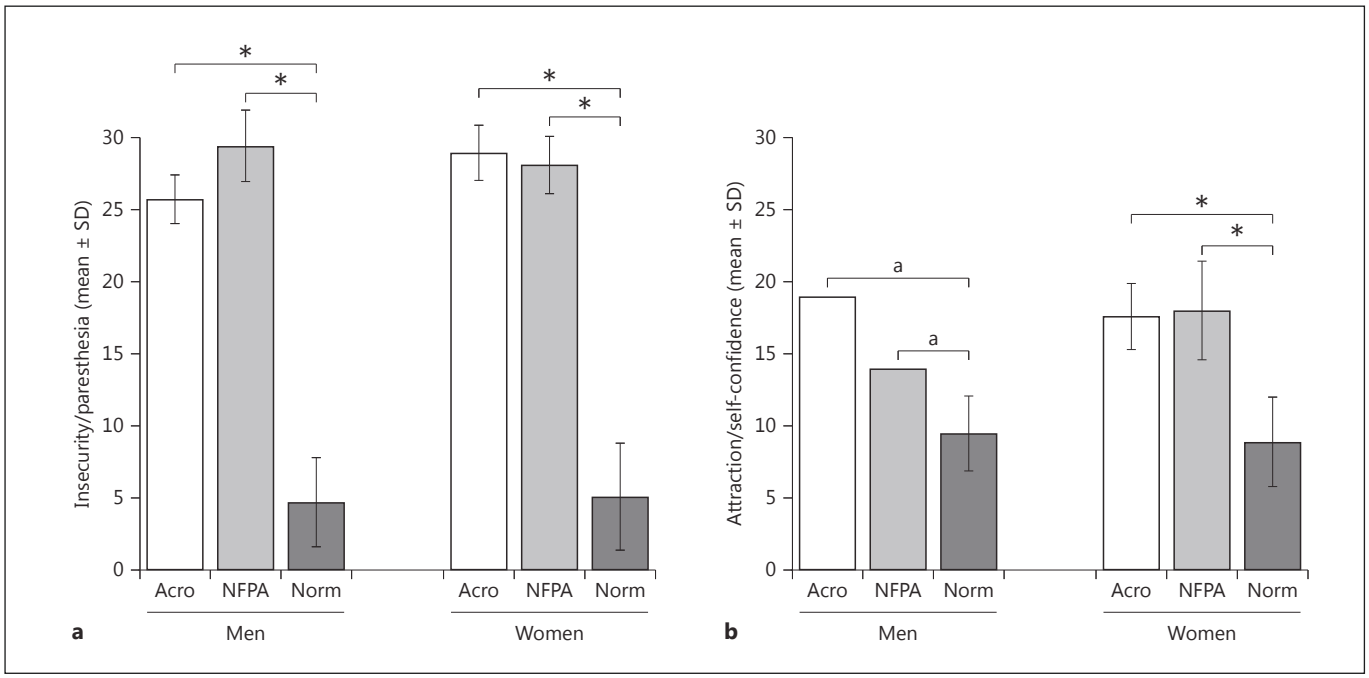
All acromegalic patients underwent comprehensive cognitive testing in the domains of attention, memory and executive functions, as previously reported [9].

Statistical Analysis

All descriptive statistics are given as frequencies in percent or mean and standard deviation for different patient groups. To compare sex, age, body mass index, frequency of comorbidities and depression scores between patients with acromegaly and patients with NFPA, χ^2 tests, Mann-Whitney U tests and t tests for independent samples were used. All further analyses were controlled for differences in age between both patient groups; results of men were dissociated from results of women comparing these two groups. Differences between the two patient groups were evaluated with analyses of covariance (ANCOVA), and the deviation of the patient scores from the respective normative values according to the manuals of the questionnaires [10, 14] were analyzed using one-sample t tests.

Moreover, for the FKB-20, we tested differences in body image perception for patients without depression (BDI-II <10), patients with mild or moderate depression (10 ≤ BDI-II < 18) and clinical depression (BDI-II ≥18) by ANCOVA. Furthermore, we analyzed differences in body image perception between acromegalic patients with cognitive impairment – defined as a percentile ranking <16 – and those with normal cognition using t tests.

In addition, in a subgroup of patients with acromegaly (n = 39), we tested whether different degrees of disease severity (expert



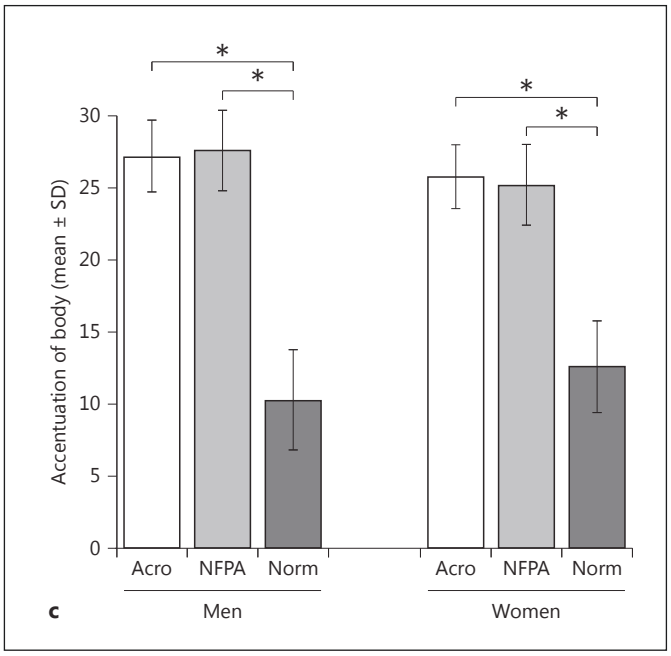


Fig. 1. Comparisons between patients with acromegaly (Acro, men: n = 31, women: n = 38), patients with NFPA (men: n = 35, women: n = 20) and norm values of students in the 'insecurity/concerns' (**a**), 'attraction/self-confidence' (**b**) and 'accentuation of the body/sensitivity' (**c**) scales of the FBeK questionnaire. SD = Standard deviation. * Groups differ significantly with $p < 0.05$. [a] Groups are too small to analyse differences because of missing data.

opinion based on photographs of the faces: mild, moderate, severe) lead to different body image perception (ANCOVA). Furthermore, we calculated whether there are differences in body image perception between patients with satisfactory treatment status (according to laboratory values) and those who are biochemically uncontrolled by t tests. Data analysis was performed with SPSS 20 and R 3.1.0.

Results

Patient Demographics

Clinical characteristics of the study population are shown in table 1. There were significant differences between the acromegalic and the NFPA patient groups in the following characteristics: sex (p = 0.033), age (p =

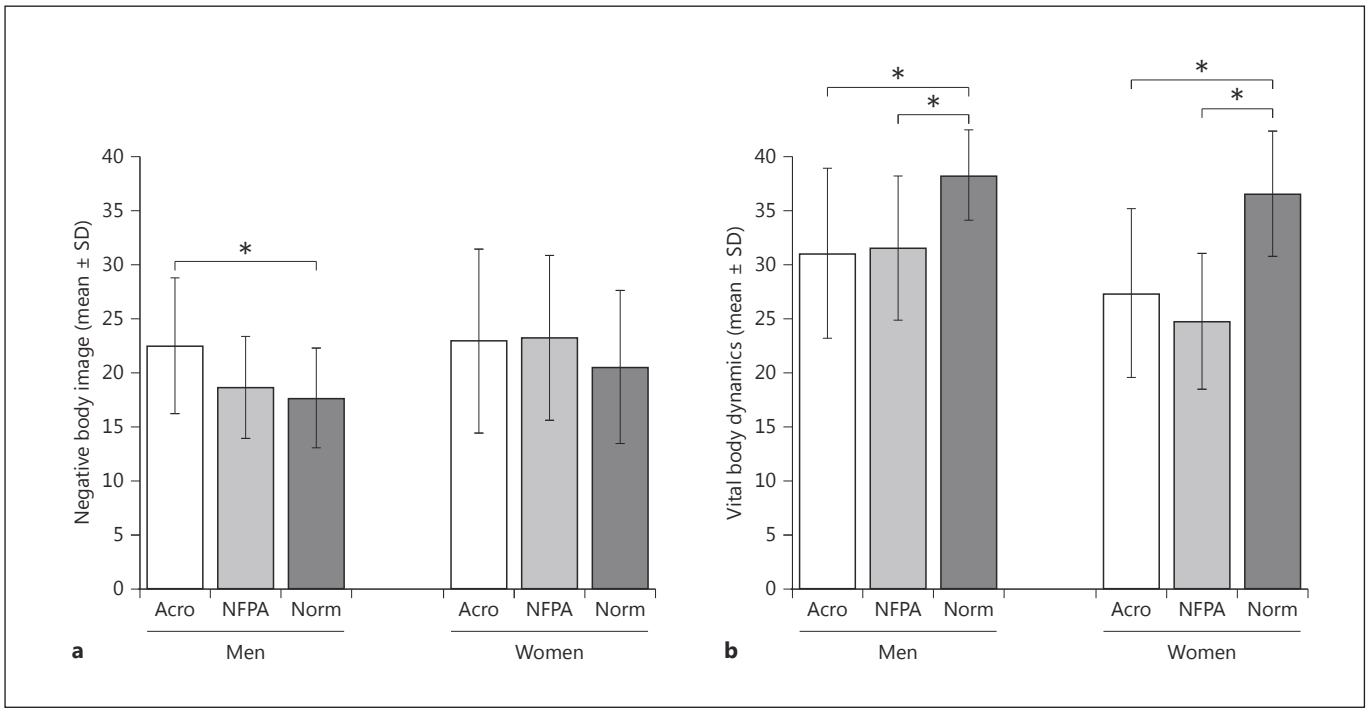


Fig. 2. Comparisons between patients with acromegaly (Acro), patients with NFPA and norm values of students in the 'negative body image' (**a**) and 'vital body dynamics' (**b**) scales of the FKB-20 questionnaire. SD = Standard deviation. * Groups differ significantly with $p < 0.05$. Note: For negative body image, lower values equal reduced self-perception; for vital body dynamics, higher values equal improved self-perception.

0.023), arrhythmia ($p = 0.022$), cardiomyopathy ($p = 0.011$), arthralgia ($p = 0.014$), carpal tunnel syndrome ($p = 0.002$), diabetes mellitus ($p = 0.018$), pathological glucose intolerance ($p < 0.001$), pituitary insufficiency ($p = 0.001$) and sleep apnea ($p = 0.002$). Therefore, effects comparing these two groups were estimated controlling for between-group differences in age. Results of men were dissociated from results of women, respectively.

Body Image Perception in Acromegalic Patients

Compared to normative values, patients with acromegaly (both men and women) presented with a worse subjective body image, showing significantly more 'insecurity/paresthesia' ($p < 0.001$) and more 'accentuation of the body' ($p < 0.001$) according to the FBeK. Interestingly, acromegalic women scored significantly higher in the 'attraction/self-confidence' scale (17.6 ± 2.3 vs. 9 ± 3.1; $p < 0.001$) (fig. 1).

Additionally, acromegalic men showed significantly worse subjective body image (higher mean values in the 'negative body image' scale of the FKB-20; 22.5 ± 6.3 vs. 18 ± 4.6; $p < 0.001$), whereas both acromegalic men and women showed significantly lower vitality as indicated by lower mean values in the 'vital body dynamics' scale of the FKB-20 (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) (fig. 2).

Body Image Perception in Acromegalic Patients versus NFPA Patients

There were no significant differences between acromegalic patients and patients with NFPA (both groups divided into men and women) in any of the three FBeK subscales (fig. 1).

Acromegalic patients differed significantly from NFPA patients only regarding vitality as judged by the 'vital body dynamics' scale of the FKB-20 questionnaire ($F = 5.040$, $p = 0.003$), whereby women with NFPA showed the lowest vitality (24.8 ± 6.3) and men with NFPA the highest vitality (31.6 ± 6.7) (fig. 2).

Association of Negative Body Image with Depression

We further analyzed associations for negative body image in patients with acromegaly (and NFPA) with other potentially causal factors. For the FKB-20, we tested

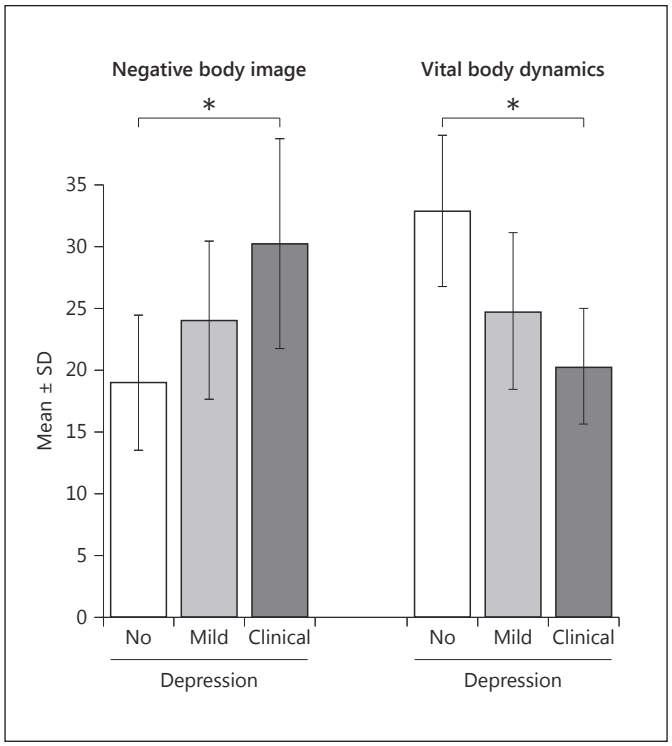


Fig. 3. Differences between patients without depression, patients with mild or moderate depression and patients with clinical depression in the 'negative body image' and 'vital body dynamics' scales of the FKB-20 questionnaire. SD = Standard deviation. * Groups differ significantly with $p < 0.05$. Note: For negative body image, lower values equal reduced self-perception; for vital body dynamics, higher values equal improved self-perception.

differences in body image perception for patients without depression (BDI-II <10), patients with mild or moderate depression (10 ≤ BDI-II < 18) and patients with clinical depression as indicated by BDI-II ≥18. Indeed, patients with clinical depression (BDI-II ≥18) showed significantly lower body vitality ($F = 29.967$, $p < 0.001$) and significantly worse subjective body image ($F = 20.293$, $p < 0.001$), according to the FKB-20 (fig. 3).

Association of Negative Body Image with Cognitive Status

We went on to test whether negative body image might also be attributed to cognitive decline and analyzed differences in body image perception between acromegalic patients with cognitive impairment – defined as a percentile ranking <16 – and those with normal cognitive status; however, we could not detect any significant differences between the two groups.

Correlation of Negative Body Image with Objective Acromegalic Changes as Judged by Medical Experts (Visual Disease Severity)

In a subgroup of acromegalic patients with available frontal and side photographs of the faces (n = 39), we grouped patients into subjects with mild (n = 14), moderate (n = 19) and severe acromegaly (n = 6) by expert opinion and tested whether different degrees of disease severity might lead to a more negative body image. However, we could not detect any significant correlations between visual disease severity and negative body image (table 2). Moreover, there were no significant differences in negative body image between patients with satisfactory treatment status according to laboratory values and those who were biochemically uncontrolled or dependent on duration of biochemical control.

Discussion

In this study, we investigated a lack of subjective perception of the disease state in acromegaly as a potential explaining factor for the late diagnosis of up to 10 years for this disease. We found that patients with acromegaly do not lack subjective perception of the disease state, compared to normal controls. Body image perception of NFPA patients does not differ from patients with acromegaly, although these patients hardly exhibit any physical/bodily changes. Negative body image correlated with depression, though was not different between patients with different severity grades of the disease or biochemical control.

Our results are in accordance with previous studies reporting disturbed body image perception in patients with acromegaly [4, 5]. Recent articles on appearance and self-image in acromegaly show that the persistence of body image disturbances even after long-term biochemical control of the disease might relate to persistence of facial deformities [19, 20]. Moreover, our results correspond to our former work, showing that patients with acromegaly burden high neuropsychiatric morbidity including high prevalence of affective disorders [7], macroscopic brain architecture changes [21], anxiety-related personality traits [22], cognitive dysfunction [9] and pain syndromes [23]. Tiemensma et al. [24] have also documented affected illness perceptions in acromegalic patients even after long-term remission of the disease, and recently, increased psychosocial impairment has been linked to diagnostic delay in acromegaly [25]. However, emotional disorders do not seem to burden only acromegalic patients

Table 2. Disease severity and body image perception

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.

but also patients with other types of pituitary adenomas, affecting the diagnostic process, as was the case in our NFPA control population [3].

We can only speculate as to why modifiable factors such as biochemical control, duration of disease remission and disease severity do not correlate with a more negative body image. On the one hand, chronic GH/IGF-1 excess leads – even after long-term cure of the disease – to irreversible changes in the bone, but also in the central nervous system, as we have previously shown [21]. Otherwise, it can be argued that body image disturbance is rather an 'on-off' effect which can be quantified with difficulty and once developed, is irrespective of disease severity or duration. Another explanation of the findings could be that given the very slow changes which occur in acromegaly, the patients adapt to these changes and this could be a reason why their perception of body image is not abnormal.

As a limitation of our study, we have to mention the cross-sectional design, which limits the possibility to draw conclusions on causal interferences between acromegaly-associated changes and the development of an altered body image perception. Furthermore, for the FBeK questionnaire, normative data available from the manual derive from students aged 17–31 years, who are definitely younger than the acromegalic and NFPA patients examined here.

In conclusion, patients with acromegaly suffer from negative body image, which is, however, unrelated to their objective disease state/severity and practically does not differ from patients with hardly any bodily changes (NFPA). This negative body image correlates with depression, though not with cognitive impairment, biochemical control or duration of disease remission. Thus, extensive diagnostic and therapeutic workup of acromegalic comorbidities such as depression should be emphasized in the current treatment algorithms for acromegaly.

Acknowledgements

NeoExNET (Network of Excellence for Neuroendocrine Tumours) is a national database for the evaluation of diagnostics, treatment and outcome in neuroendocrine tumours. NeoExNET is supported by the German Federal Ministry of Education and Research (BMBF; m4 Cluster, 16EX1221J, 01EX1020E) and by an unrestricted educational grant of Novartis. Members of the NeoExNET-Study group include: principal investigator: Gunter K. Stalla (MPI of Psychiatry, Munich); steering committee: Felix Beuschlein (LMU, Munich), Christoph Auernhammer (LMU, Munich), Klaus A Kuhn (TU, Munich). This project was partly funded by an Else Kröner-Fresenius grant (2012_A103).

Disclosure Statement

C.D. received lecture fees and independent research grants from Pfizer, Ipsen and Novartis. S.M.L. and M.I. have nothing to disclose. H.J.S. received research grants, speaker fees and travel grants from Pfizer and speaker fees and travel grants from Novartis. J.S. received lecture fees from Pfizer, Ipsen and Novartis. S.R., R.K. and R.F. have nothing to disclose. G.K.S. received lecture fees from Pfizer, Novo Nordisk, Ipsen and Novartis. C.S. received lecture fees and independent research grants from Pfizer and Novartis.

References

1 Melmed S: Medical progress: acromegaly. N Engl J Med 2006;355:2558–2573.
2 Holdaway IM, Rajasoorya C: Epidemiology of acromegaly. Pituitary 1999;2;29–41.
3 Flitsch J, Spitzner S, Ludecke DK: Emotional disorders in patients with different types of pituitary adenomas and factors affecting the diagnostic process. Exp Clin Endocrinol Diabetes 2000;108:480–485.
4 Ezzat S: Living with acromegaly. Endocrinol Metab Clin North Am 1992;21:753–760.
5 Pantanetti P, Sonino N, Arnaldi G, Boscaro M: Self image and quality of life in acromegaly. Pituitary 2002;5:17–19.
6 Tiemensma J, Biermasz NR, van der Mast RC, Wassenaar MJ, Middelkoop HA, Pereira AM, Romijn JA: Increased psychopathology and maladaptive personality traits, but normal cognitive functioning, in patients after long-term cure of acromegaly. J Clin Endocrinol Metab 2010;95:E392–E402.
7 Sievers C, Dimopoulou C, Pfister H, Lieb R, Steffin B, Roemmler J, Schopohl J, Mueller M, Schneider HJ, Ising M, Wittchen HU, Stalla GK: Prevalence of mental disorders in acromegaly: a cross-sectional study in 81 acromegalic patients. Clin Endocrinol 2009;71:691–701.
8 Leon-Carrion J, Martin-Rodriguez JF, Madrazo-Atutxa A, Soto-Moreno A, Venegas-Moreno E, Torres-Vela E, Benito-López P, Gálvez MA, Tinahones FJ, Leal-Cerro A: Evidence of cognitive and neurophysiological impairment in patients with untreated naive acromegaly. J Clin Endocrinol Metab 2010; 95:4367–4379.
9 Sievers C, Samann PG, Pfister H, Dimopoulou C, Czisch M, Roemmler J, Schopohl J, Stalla GK, Zihl J: Cognitive function in acromegaly: description and brain volumetric correlates. Pituitary 2012;15:350–357.
10 Clement U, Löwe B: Fragebogen zum Körperbild (FKB-20). Testmappe mit Handanweisung. Göttingen, Hogrefe, 1996.
11 Löwe B, Clement U: Der 'Fragebogen zum Körperbild (FKB-20)'. Literaturüberblick, Beschreibung und Prüfung eines Messinstrumentes. [The Body Image Questionnaire, FKB-20. Literature review, description and validation of the questionnaire]. Diagnostica 1996;42:352–376.
12 Strauss B, Appelt H: Ein Fragebogen zur Beurteilung des eigenen Körpers. Diagnostica 1983;29:145–164.
13 Strauss B, Appelt H: Erfahrungen mit einem Fragebogen zum Körpererleben; in Brähler E (ed): Körpererleben. Ein subjektiver Ausdruck von Körper und Seele. Gießen, Psychosozial-Verlag, 1995, pp 220–231.
14 Strauss B, Richter-Appelt H: Fragebogen zur Beurteilung des eigenen Körpers (FBeK). Göttingen, Hogrefe, 1996.
15 Hautzinger M, Keller F, Kühner C: BDI-II. Beck-Depressions-Inventar. Revision. 2. Auflage. Pearson Assessment, Frankfurt, 2009.
16 Katznelson L, Laws ER Jr, Melmed S, Molitch ME, Murad MH, Utz A, Wass JA; Endocrine Society. Acromegaly: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2014;99:3933–3951.
17 Chanson P, Raverot G, Castinetti F, Cortet-Rudelli C, Galland F, Salenave S; French Endocrinology Society non-functioning pituitary adenoma work-group: Management of clinically non-functioning pituitary adenoma. Ann Endocrinol (Paris) 2015;76:239–247.
18 Giustina A, Barkan A, Casanueva FF, Cavagnini F, Frohman L, Ho K, Veldhuis J, Wass J, Von Werder K, Melmed S: Criteria for cure of acromegaly: a consensus statement. J Clin Endocrinol Metab 2000;85:526–529.
19 Wagenmakers MA, Roerink SH, Maal TJ, Pelleboer RH, Smit JW, Hermus AR, Bergé SJ, Netea-Maier RT, Xi T: Three-dimensional facial analysis in acromegaly: a novel tool to quantify craniofacial characteristics after long-term remission. Pituitary 2015;18:366–375.
20 Roerink SH, Wagenmakers MA, Wessels JF, Sterenborg RB, Smit JW, Hermus AR, Netea-Maier RT: Persistent self-consciousness about facial appearance, measured with the Derriford appearance scale 59, in patients after long-term biochemical remission of acromegaly. Pituitary 2015;18:126–134.
21 Sievers C, Samann PG, Dose T, Dimopoulou C, Spieler D, Roemmler J, Schopohl J, Mueller M, Schneider HJ, Czisch M, Pfister H, Stalla GK: Macroscopic brain architecture changes and white matter pathology in acromegaly: a clinicoradiological study. Pituitary 2009;12: 177–185.
22 Sievers C, Ising M, Pfister H, Dimopoulou C, Schneider HJ, Roemmler J, Schopohl J, Stalla GK: Personality in patients with pituitary adenomas is characterized by increased anxiety-related traits: comparison of 70 acromegalic patients with patients with non-functioning pituitary adenomas and age- and gender-matched controls. Eur J Endocrinol 2009;160: 367–373.
23 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;171:581–591.
24 Tiemensma J, Kaptein AA, Pereira AM, Smit JW, Romijn JA, Biermasz NR: Affected illness perceptions and the association with impaired quality of life in patients with long-term remission of acromegaly. J Clin Endocrinol Metab 2011;96:3550–3558.
25 Siegel S, Streetz-van der Werf C, Schott JS, Nolte K, Karges W, Kreitschmann-Andermahr I: Diagnostic delay is associated with psychosocial impairment in acromegaly. Pituitary 2013;16:507–514.

7. LITERATURVERZEICHNIS

Allolio, B., & Schulte, H. M. H. (2010). *Praktische Endokrinologie* (2. Auflage). München: Urban & Fischer.

Biermasz, N. R., Joustra, S. D., Donga, E., Pereira, A. M., van Duinen, N., van Dijk, M., . . . Romijn, J. A. (2011). Patients Previously Treated for Nonfunctioning Pituitary Macroadenomas Have Disturbed Sleep Characteristics, Circadian Movement Rhythm, and Subjective Sleep Quality. *Journal of Clinical Endocrinology & Metabolism, 96*(5), 1524-1532. doi: 10.1210/jc.2010-2742

Biermasz, N. R., van Thiel, S. W., Pereira, A. M., Hoftijzer, H. C., van Hemert, A. M., Smit, J. W. A., . . . Roelfsema, F. (2004). Decreased quality of life in patients with acromegaly despite long-term cure of growth hormone excess. *Journal of Clinical Endocrinology & Metabolism, 89*(11), 5369-5376. doi: 10.1210/jc.2004-0669

Copinschi, G., Nedeltcheva, A., Leproult, R., Morselli, L. L., Spiegel, K., Martino, E., . . . Van Cauter, E. (2010). Sleep Disturbances, Daytime Sleepiness, and Quality of Life in Adults with Growth Hormone Deficiency. *Journal of Clinical Endocrinology & Metabolism, 95*(5), 2195-2202. doi: 10.1210/jc.2009-2080

Dimopoulou, C., Athanasoulia, A. P., Hanisch, E., Held, S., Sprenger, T., Toelle, T. R., . . . Sievers, C. (2014). Clinical characteristics of pain in patients with pituitary adenomas. *European Journal of Endocrinology, 171*(5), 581-591. doi: 10.1530/eje-14-0375

Dimopoulou, C., Ising, M., Pfister, H., Schopohl, J., Stalla, G. K., & Sievers, C. (2013). Increased Prevalence of Anxiety-Associated Personality Traits in Patients with Cushing's Disease: A Cross-Sectional Study. *Neuroendocrinology, 97*(2), 139-145. doi: 10.1159/000338408

Dimopoulou, C., Leistner, S. M., Ising, M., Schneider, H. J., Schopohl, J., Rutz, S., . . . Sievers, C. (2017). Body Image Perception in Acromegaly Is Not Associated with Objective Acromegalic Changes but Depends on Depressive Symptoms. *Neuroendocrinology, 105*(2), 115-122. doi: 10.1159/000448519

Ezzat, S. (1992). Living with acromegaly. *Endocrinology & Metabolism Clinics of North America, 21*(3), 753-760.

Ezzat, S., Asa, S. L., Couldwell, W. T., Barr, C. E., Dodge, W. E., Vance, M. L., & McCutcheon, I. E. (2004). The prevalence of pituitary adenomas: a systematic review. *Cancer, 101*(3), 613-619. doi: 10.1002/cncr.20412

Fernandez, A., Karavitaki, N., & Wass, J. A. (2010). Prevalence of pituitary adenomas: a community-based, cross-sectional study in Banbury (Oxfordshire, UK). *Clinical Endocrinology (Oxf), 72*(3), 377-382. doi: 10.1111/j.1365-2265.2009.03667.x

Heald, A. H., Ghosh, S., Bray, S., Gibson, C., Anderson, S. G., Buckler, H., & Fowler, H. L. (2004). Long-term negative impact on quality of life in patients with successfully treated Cushing's disease. *Clinical Endocrinology, 61*(4), 458-465. doi: 10.1111/j.1365-2265.2004.02118.x

Holdaway, I. M., & Rajasoorya, C. (1999). Epidemiology of acromegaly. *Pituitary, 2*(1), 29-41.

Johnson, M. D., Woodburn, C. J., & Vance, M. L. (2003). Quality of life in patients with a pituitary adenoma. *Pituitary, 6*(2), 81-87.

Kelly, W. F. (1996). Psychiatric aspects of Cushing's syndrome. *QJM, 89*(7), 543-551.

Leistner, S., Dimopoulou, C., Athanasoulia, A., Roemmler-Zehrer, J., Schopohl, J., Stalla, G. K., & Sievers, C. (2015). Higher state- and trait-anxiety in patients with pituitary adenomas compared to norm values of healthy controls. *Experimental & Clinical Endocrinology & Diabetes, 123*(03), P02_01. doi: 10.1055/s-0035-1547624

Leistner, S. M., Klotsche, J., Dimopoulou, C., Athanasoulia, A. P., Roemmler-Zehrer, J., Pieper, L., . . . Sievers, C. (2015). Reduced sleep quality and depression associate with decreased quality of life in patients with pituitary adenomas. *Eur J Endocrinol, 172*(6), 733-743. doi: 10.1530/eje-14-0941

Leon-Carrion, J., Martin-Rodriguez, J. F., Madrazo-Atutxa, A., Soto-Moreno, A., Venegas-Moreno, E., Torres-Vela, E., . . . Leal-Cerro, A. (2010). Evidence of cognitive and neurophysiological impairment in patients with untreated naive acromegaly. *Journal of Clinical Endocrinology & Metabolism, 95*(9), 4367-4379. doi: 10.1210/jc.2010-0394

McDowell, B. D., Wallace, R. B., Carnahan, R. M., Chrischilles, E. A., Lynch, C. F., & Schlechte, J. A. (2011). Demographic differences in incidence for pituitary adenoma. *Pituitary, 14*(1), 23-30. doi: 10.1007/s11102-010-0253-4

Melmed, S. (2006). Medical progress: Acromegaly. *New England Journal of Medicine, 355*(24), 2558-2573. doi: 10.1056/NEJMra062453

Mouthaan, J., Sijbrandij, M., Luitse, J. S., Goslings, J. C., Gersons, B. P., & Olff, M. (2014). The role of acute cortisol and DHEAS in predicting acute and chronic PTSD symptoms. *Psychoneuroendocrinology, 45*, 179-186. doi: 10.1016/j.psyneuen.2014.04.001

Paisley, A. N., Rowles, S. V., Roberts, M. E., Webb, S. M., Prieto, B. L., Shalet, S. M., & Trainer, P. J. (2007). Treatment of acromegaly improves quality of life, measured by AcroQol. *Clinical Endocrinology, 67*(3), 358-362. doi: 10.1111/j.1365-2265.2007.02891.x

Pantanetti, P., Sonino, N., Arnaldi, G., & Boscaro, M. (2002). Self image and quality of life in acromegaly. *Pituitary, 5*(1), 17-19.

Pereira, A. M., Tiemensma, J., & Romijn, J. A. (2010). Neuropsychiatric Disorders in Cushing's Syndrome. *Neuroendocrinology, 92*, 65-70. doi: 10.1159/000314317

Saeger, W., Ludecke, D. K., Buchfelder, M., Fahlbusch, R., Quabbe, H. J., & Petersenn, S. (2007). Pathohistological classification of pituitary tumors: 10 years of experience with the German Pituitary Tumor Registry. *European Journal of Endocrinology, 156*(2), 203-216. doi: 10.1530/eje.1.02326

Sievers, C., Dimopoulou, C., Pfister, H., Lieb, R., Steffin, B., Roemmler, J., . . . Stalla, G. K. (2009). Prevalence of mental disorders in acromegaly: a cross-sectional study in 81 acromegalic patients. *Clinical Endocrinology, 71*(5), 691-701. doi: 10.1111/j.1365-2265.2009.03555.x

Sievers, C., Samann, P. G., Pfister, H., Dimopoulou, C., Czisch, M., Roemmler, J., . . . Zihl, J. (2012). Cognitive function in acromegaly: description and brain volumetric correlates. *Pituitary, 15*(3), 350-357. doi: 10.1007/s11102-011-0326-z

Sonino, N., Fallo, F., & Fava, G. A. (2010). Psychosomatic aspects of Cushing's syndrome. *Reviews in Endocrine and Metabolic Disorders, 11*(2), 95-104. doi: 10.1007/s11154-009-9123-7

Tiemensma, J., Biermasz, N. R., Middelkoop, H. A. M., van der Mast, R. C., Romijn, J. A., & Pereira, A. M. (2010). Increased Prevalence of Psychopathology and Maladaptive Personality Traits after Long-Term Cure of Cushing's Disease. *Journal of Clinical Endocrinology & Metabolism, 95*(10), E129-E141. doi: 10.1210/jc.2010-0512

Tiemensma, J., Biermasz, N. R., van der Mast, R. C., Wassenaar, M. J. E., Middelkoop, H. A. M., Pereira, A. M., & Romijn, J. A. (2010). Increased Psychopathology and Maladaptive Personality Traits, But Normal Cognitive Functioning, In Patients after Long-Term Cure of Acromegaly. *Journal of Clinical Endocrinology & Metabolism, 95*(12), E392-E402. doi: 10.1210/jc.2010-1253

van Aken, M. O., Pereira, A. M., Biermasz, N. R., van Thiel, S. W., Hoftijzer, H. C., Smit, J. W. A., . . . Romijn, J. A. (2005). Quality of life in patients after long-term biochemical cure of Cushing's disease. *Journal of Clinical Endocrinology & Metabolism, 90*(6), 3279-3286. doi: 10.1210/jc.2004-1375

van der Klaauw, A. A., Biermasz, N. R., Pereira, A. M., van Kralingen, K. W., Dekkers, O. M., Rabe, K. F., . . . Romijn, J. A. (2008). Patients cured from craniopharyngioma or nonfunctioning pituitary macroadenoma (NFMA) suffer similarly from increased daytime somnolence despite normal sleep patterns compared to healthy controls. *Clinical Endocrinology, 69*(5), 769-774. doi: 10.1111/j.1365-2265.2008.03284.x

van der Klaauw, A. A., Kars, M., Biermasz, N. R., Roelfsema, F., Dekkers, O. M., Corssmit, E. P., . . . Romijn, J. A. (2008). Disease-specific impairments in quality of life during long-term follow-up of patients with different pituitary adenomas. *Clinical Endocrinology, 69*(5), 775-784. doi: 10.1111/j.1365-2265.2008.03288.x

van der Klaauw, A. A., Pereira, A. M., van Kralingen, K. W., Rabe, K. F., & Romijn, J. A. (2008). Somatostatin analog treatment is associated with an increased sleep latency in patients with long-term biochemical remission of acromegaly. *Growth Hormone & Igf Research, 18*(5), 446-453. doi: 10.1016/j.ghir.2008.04.001

Webb, S. M. (2006). Quality of life in acromegaly. *Neuroendocrinology, 83*(3-4), 224-229. doi: 10.1159/000095532

8. DANKSAGUNG

Mein besonderer Dank gilt meiner Doktorarbeitsbetreuerin PD Dr. Caroline Jung-Sievers: Bereits während meines Diplom-Studiums durfte ich unter ihrer Betreuung erste wissenschaftliche Erfahrungen in der Arbeitsgruppe „Neuroendokrinologie“ des Max-Planck-Instituts für Psychiatrie sammeln, später stellte sie neben einer sehr geduldigen Betreuerin meiner Doktorarbeit während zahlreicher Nebenschauplätzen (klinische Tätigkeit und Ausbildung) ebenso stets eine sehr wichtige Beraterin in beruflichen Fragen dar, deren Meinung und Wissen sowie warmherzige Art dabei man nicht missen mag.

Ebenso danken möchte ich Personen, ohne deren Vertrauen und Unterstützung ich die Möglichkeit zu dieser Dissertation nicht erhalten hätte:
Allen voran herzlichen Dank an meinen Doktorvater Herrn Prof. Stalla, der diese Arbeit und schließlich auch mir damit viel ermöglicht hat, letztendlich auch die inzwischen mehr als achtjährige Tätigkeit am Max-Planck-Institut für Psychiatrie in München.
Vielen Dank auch an Herrn Prof. Wittchen, den ich während eines sehr interessanten Forschungspraktikums in Dresden schließlich vor einigen Jahren auch selbst kennenlernen durfte.
Besondere Geduld zeigte Frau Dr. Stephany Fulda, die mir meine ersten R-Kenntnisse vermittelte. Dank ihr habe ich weiterhin eine große Begeisterung an Statistik sowie Theaterbesuchen, wieso ich mich stets gerne an die gemeinsame Zeit „im Schlaflabor“ erinnern werde.
Herzlichen Dank auch an Herrn Prof. Keck und Dr. Pierre Beitinger, die während meiner klinischen Tätigkeit die Fertigstellung meiner Dissertation immer gefördert haben.

Ein besonders herzlicher Dank geht an meine Familie, die die langen Jahre der Promotion und Ausbildung ermöglicht und unterstützt haben sowie immer wieder Verständnis dafür aufbringen, dass manchmal wenig Zeit für andere Dinge bleibt. Ebenso

bedanken möchte ich mich an dieser Stelle bei meinen Freunden, allen voran bei Herrn Tobias Bauer.

Meinem Partner – Herrn Frederik Quaatz – danke ich sehr für seine stets liebevollen und unterstützenden Worte auf dem langen Weg, aber auch für die tatkräftigen Korrektur- und Layouthilfen und allem voran für den so starken Rückhalt während dieser Zeit. Lieben Dank!

9. LEBENSLAUF

Persönliche Daten

Name: Sarah Miriam Leistner

Geburtstag: 18.08.1986
Familienstand: ledig

Therapeutische Aus- und Weiterbildung und klinische Tätigkeit

seit 03/15	**VFKV-Ausbildungsinstitut München** Beginn der Weiterbildung „Schematherapie“ (mit Zertifizierung)
ab 04/16	Fortführung der Ausbildung zur psychologischen Psychotherapeutin im Richtlinienverfahren Verhaltenstherapie (Schwerpunkt Erwachsene)
seit 07/14	**Max-Planck-Institut für Psychiatrie München** Wissenschaftliche Angestellte auf Station 3 (OA Dr. Ditzen); bis 07/16 im Rahmen der praktischen Ausbildung
ab 01/16	Leitung und Koordination des MPG-finanzierten Projektes „RefPsych“ zur Flüchtlingshilfe und Psychoedukation von Helfern
01/14 – 06/14	**Danuvius-Klinik Pfaffenhofen** Diplom-Psychologin auf der Kriseninterventionsstation (OA Dr. Tiltscher) im Rahmen der praktischen Ausbildung
07/13 – 03/16	**DGVT-Ausbildungsakademie München** Beginn der Ausbildung zur psychologischen Psychotherapeutin im Richtlinienverfahren Verhaltenstherapie (Schwerpunkt Erwachsene)

Wissenschaftlicher Werdegang

seit 05/13	**Max-Planck-Institut für Psychiatrie München** Beginn der Promotion (Dr. rer. biol. hum.) bei Prof. Stalla in der Arbeitsgruppe „Klinische Neuroendokrinologie”

10/13 – 03/16 **Ludwig-Maximilians-Universität München**
Lehrbeauftragte des Masterstudiengangs „Klinische Psychologie und kognitive Neurowissenschaften“ für den Lehrstuhl Allgemeine Psychologie II (Prof. Maier)

10/12 – 09/13 **Katholische Universität Eichstätt/Ingolstadt**
Wissenschaftliche Mitarbeiterin am Lehrstuhl für Klinische und Biologische Psychologie (Prof. Rosner)

Studium

10/07 – 09/12 **Ludwig-Maximilians-Universität München**
Studiengang **Diplompsychologie**

Vordiplom seit September 2009
Schwerpunkte Hauptstudium: Klinische Neuropsychologie und Klinische Psychologie & Psychotherapie
Diplomarbeit am Lehrstuhl für Klinische Psychologie & Psychotherapie in Zusammenarbeit mit der psychosomatischen Klinik Bad Grönenbach über die Prädiktion von Angststörungsdiagnosen durch psychometrische Testskalen
Diplom: seit September 2012 (Gesamtnote: 1.18)

10/08 – 09/12 **Ludwig-Maximilians-Universität München**
Studiengang **Germanistik und Sozialkunde (Lehramt Gymnasium)**

Zwischenprüfungen seit September 2010

Studienbegleitende wissenschaftliche Tätigkeiten & Praktika

03/10 – 09/12 **Max-Planck-Institut für Psychiatrie, München**
Mitarbeit als Gast in der AG Stalla (Klinische Neuroendokrinologie)

02/11 – 04/11 **Medizinisch-Psychosomatische Klinik Roseneck, Prien am Chiemsee**
8-wöchiges klinisches Praktikum

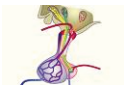
09/10 – 10/10 **Institut für Klinische Psychologie und Psychotherapie, TU Dresden**
6-wöchiges Forschungspraktikum am Institut von Prof. Wittchen

Schulbildung

09/97 – 06/06 **Camerloher-Gymnasium, Freising**
Abschluss: Abitur (Gesamtnote: 1,3)

ANHANG

RG Clinical Neuroendocrinology



STATE- AND TRAIT-ANXIETY IN PATIENTS WITH PITUITARY ADENOMAS

MAX-PLANCK-GESELLSCHAFT

Leistner, S.M.[1], Dimopoulou, Ch.[1], Athanasoulia, A.P. [1], Roemmler-Zehrer, J.[2], Schopohl, J.[2], Stalla, G.K.[1], Sievers, C.[1]

Context: Several studies reported psychiatric symptoms, e.g. increased rates of depression, for patients with pituitary adenomas.

Objective: Our aim was to explore state- and trait-anxiety in patients with different pituitary adenomas. Moreover we compared patient' anxiety values to norm values of healthy controls.

Methods

Setting:

Endocrine Outpatient Unit of the Max-Planck-Institute of Psychiatry and the Department of Internal Medicine, Ludwig-Maximilians-University, Munich.

Participants:

- patients with Acromegaly ($n = 69$)
- patients with Non-functioning-pituitary-adenomas (NFMA) ($n = 58$)
- patients with Cushing disease ($n = 64$)
- patients with Prolactinoma ($n = 79$)
- norm values of healthy adults ($n = 1488$)

Main Outcome Measure(s):

- Depression: Beck-Depression-Inventory (BDI)
- State- and trait-anxiety: State-Trait-Anxiety-Inventory (STAI)

Statistical analysis:

- Chi^2-Tests
- ANOVA, ANCOVA
- t-test for one sample

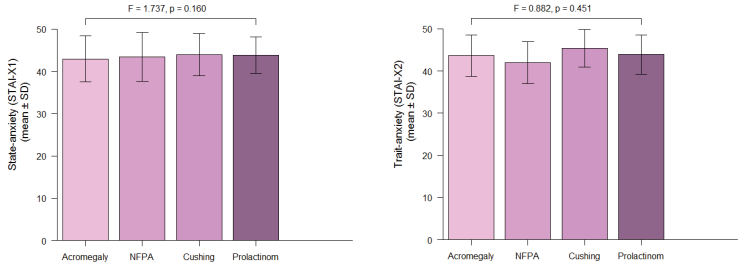
All differences between the four patient groups were controlled for differences in sex, age, BMI, duration of hormonal excess and depression.

Results

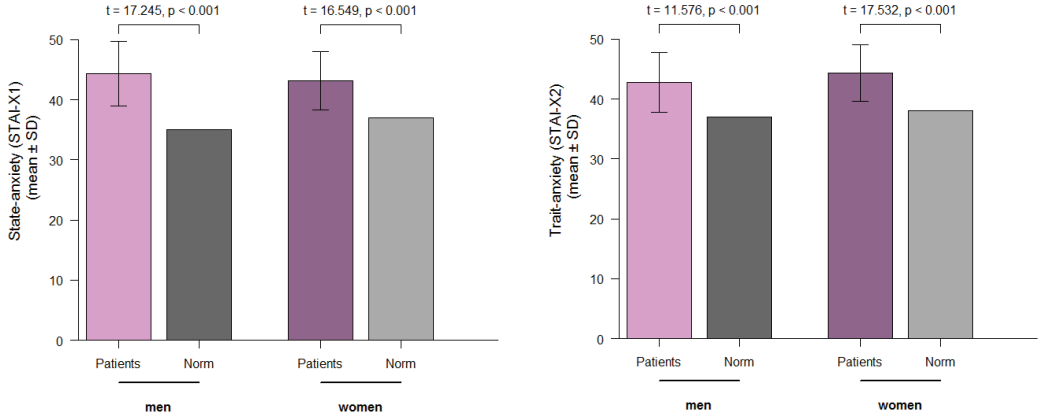
1. Differences between patient groups

	Groups				Effect	
	Acromegaly $n = 69$	**Non-functioning pituitary adenomas** $n = 58$	**Cushing disease** $n = 64$	**Prolactinoma** $n = 79$	Test-statistic	*p-value*
Sex (male/female, n (%))	30/39 (43.5/56.5)	38/20 (65.5/34.5)	13/51 (20.3/79.7)	18/61 (22.8/77.2)	$\chi^2 = 36.094$	**< 0.001**
Age (years, mean±SD)	54.96 (11.04)	60.50 (10.15)	50.14 (11.51)	50.89 (12.87)	$F = 10.566$	**< 0.001**
BMI (kg/m^2, mean±SD)	29.02 (5.48)	28.57 (5.11)	26.00 (5.30)	25.31 (6.77)	$F = 7.096$	**< 0.001**
Primary adenoma type						
Micro (%)	10.1	6.9	26.6	48.1		
Macro (%)	66.7	82.8	14.1	48.1	$\chi^2 = 115.24$	**< 0.001**
Unknown size (%)	23.2	10.3	59.4	3.8		
Biochemically controlled (%)[a]	65.2	-	62.5	69.6	$\chi^2 = 0.830$	0.660
Duration of hormonal excess (months, mean±SD)	261.2 (118.9)	-	174.2 (98.0)	238.9 (84.6)	$F = 12.534$	**< 0.001**
Comorbidities						
Cardiovascular disease (%)	33.3	8.6	20.3	15.2	$\chi^2 = 13.675$	**0.003**
Diabetes mellitus (%)	27.5	10.3	17.2	3.8	$\chi^2 = 17.995$	**< 0.001**
Pulmonary disease (%)	7.2	1.7	9.4	12.7	$\chi^2 = 5.549$	0.136
Hypertension (%)	55.1	43.1	56.3	20.3	$\chi^2 = 25.407$	**< 0.001**
Depression						
BDI[1] (mean±SD)	8.97 (8.58)	8.05 (7.20)	13.80 (10.19)	9.38 (9.58)	$F = 5.099$	**0.002**

BMI: body mass index, BDI: Beck-Depression -Inventory, SD: standard deviation
[a] according to laboratory values
[1] = hiaher values equal hiather score in deression



2. Differences between patients with pituitary adenomas and norm values of healthy controls



Conclusions

These findings emphasize the importance of diagnosing and treating psychiatric symptoms as anxiety in patients with pituitary adenomas.

[1] Max-Planck-Institute for Psychiatry (MPI), [2] Departement of Internal Medicine (LMU)