NEBENSCHILDDRÜSE

&

PSYCHE

KARIN AMREIN

VORTRAG MIT FREUNDLICHER UNTERSTÜTZUNG DER FA. SHIRE

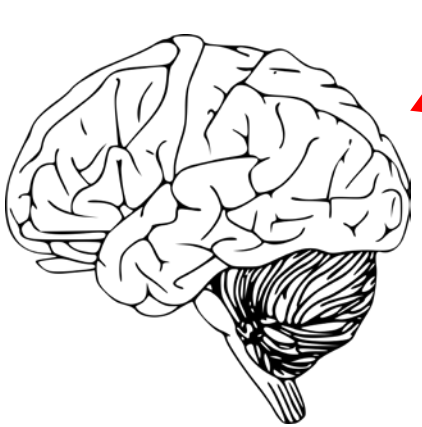
DIESER VORTRAG SPIEGELT ABER NICHT UNBEDINGT DIE MEINUNG VON SHIRE WIDER

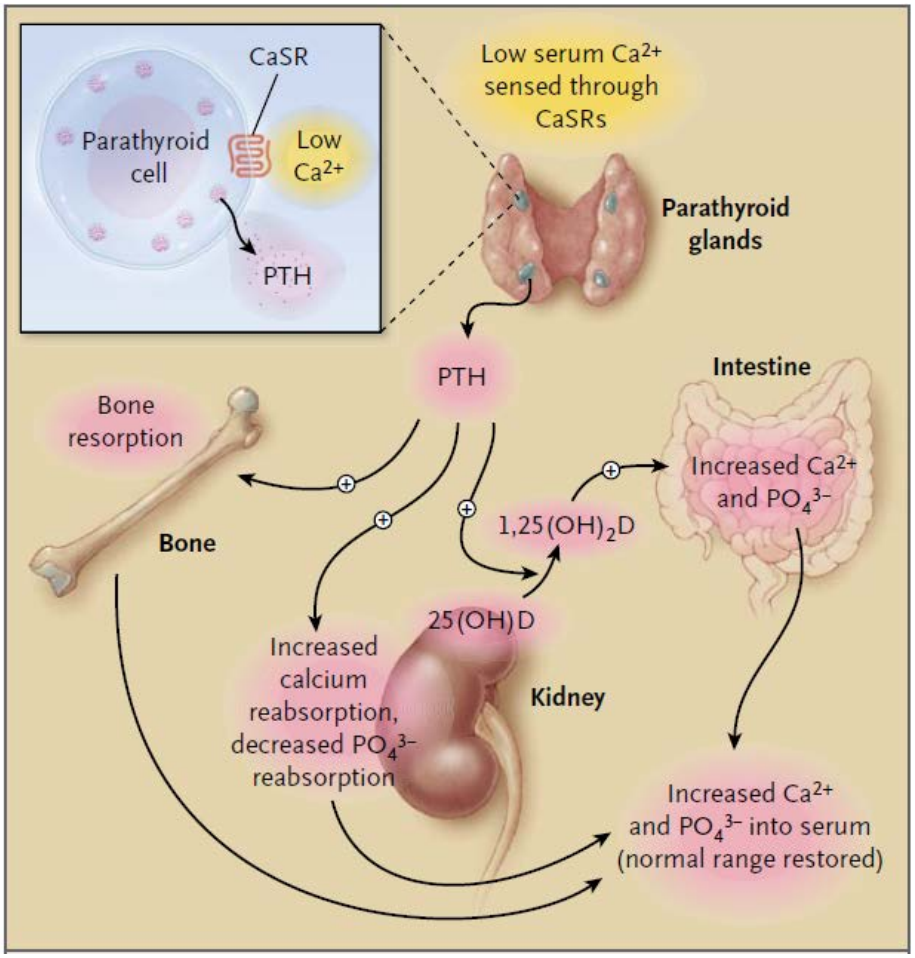
DISCLOSURES/ CONFLICTS OF INTEREST

DIE SPRECHER ERHIELT HONORARE FÜR VORTRÄGE, BERATERTÄTIGKEIT, KONGRESSUNTERSTÜTZUNG ETC. VON:

SHIRE
FRESENIUS
BBRAUN
SINAPHARM
SIEMENS

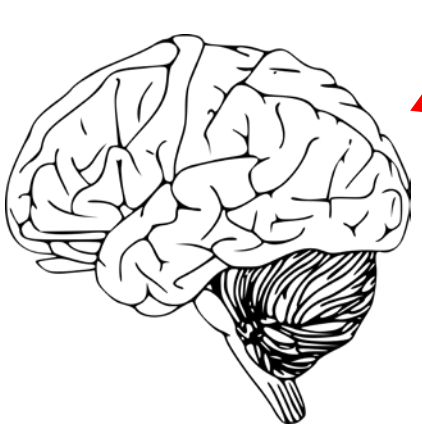
PTH - Wirkung

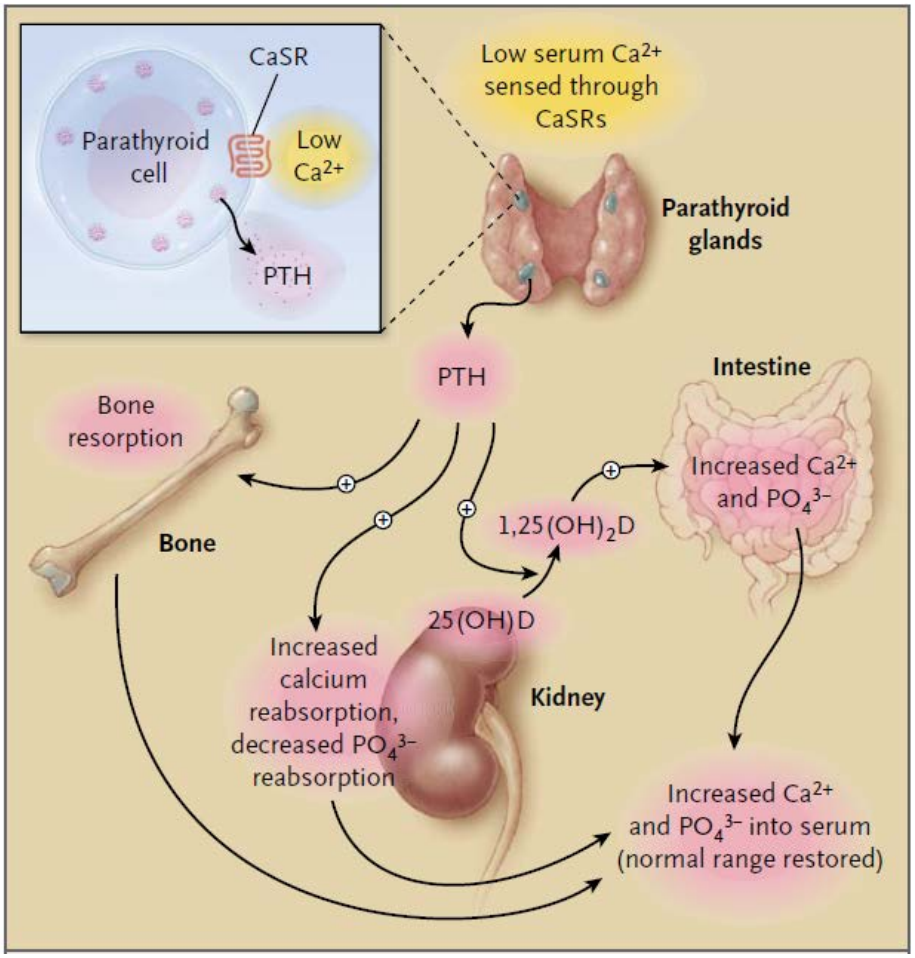




Shoback D NEJM 2008

PTH - Wirkung





Shoback D NEJM 2008

HYPOPARA

HYPERPARA

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Neurological Complications of Herpes Simplex Virus Type 2 Infection
Clinical Implications of Basic Neuroscience Research | May 1, 2008
Biomarker Results in Patients With Mild Cognitive Impairment
Original Investigation | October 16, 2017

This Issue

Article

April 1964

More

Neuropsychiatric Disorders in Primary Hyperparathyroidism

Clinical Analysis With Review of the Literature

GEORGE KARPATI, MD; BOY FRAME, MD

Author Affiliations

Arch Neurol. 1964;10(4):387-397. doi:10.1001/archneur.1964.00460160057005

Full Text

Abstract

Endocrine disorders are being more frequently recognized as causes for significant mental and neuromuscular manifestations, which often dominate the clinical picture. Among these endocrinopathies hyperthyroidism, myxedema, diabetes mellitus hyperinsulinism, Cushing's disease, Addison's disease,

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May 1, 2008

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Biomarker Results in Patients With Mild Cognitive Impairment
October 16, 2017

NEUROPSYCHIATRIC DISEASE

- Symptoms Depend On The
- Rise Of Serum Calcium Level And Include
  - Cognitive Dysfunction,
  - Depression
  - Lethargy

  - With Severe Hypercalcemia (Parathyroid crisis)
    - Psychosis
    - Coma

Gasser R WKW 2013, Pallan S BMJ 2012

QUALITY OF LIFE IN PRIMARY HYPERPARA

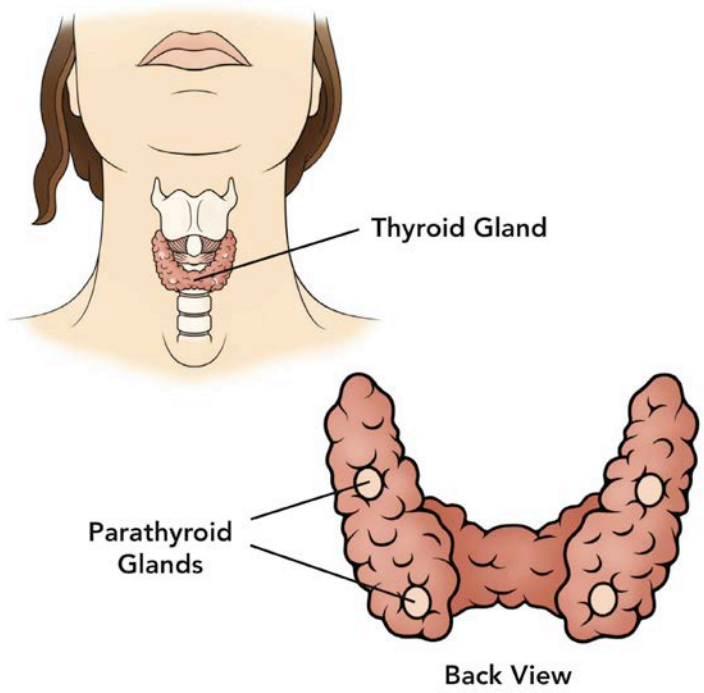
- not yet considered as typical feature of the disease and not included in the guidelines for surgery

- Pat. experience early nonspecific symptoms
  - Weakness
  - Depression
  - sleep disturbance
  - memory loss
  - Anxiety
- Possible improvement of quality of life and well-being after surgery

Cipriani C Expert Rev Pharmacoecon Outcomes Res 2014

Hypoparathyroidism

Die **letzte** klassische Endokrinopathie ohne Hormonersatz...!?!



Hormone Health NETWORK
Keep your body in balance

- **Keine kausale** Standard-Therapie
- Symptomatisch (Calcium, Calcitriol, Vitamin D, Magnesium, Thiazide)

- **Häufig Symptome trotz Therapie**
- Tetanie, Parästhesie, Muskelschwäche, „Brain Fog“

- **Eingeschränkte Lebensqualität (QoL) -> unterschätzt![1]**
- Empathy Gap!
- Schwere Symptomatik -> keine Arbeitsfähigkeit, eingeschränkte Alltagsbewältigung

1) Cho N et al.: Surgeons and patients disagree on the potential consequences from hypoparathyroidism. Endocrine Practice 2014

The NEW ENGLAND JOURNAL of MEDICINE

IMAGES IN CLINICAL MEDICINE

Chvostek's and Trousseau's Signs

A 38-YEAR-OLD MAN PRESENTED TO THE EMERGENCY DEPARTMENT WITH

Jesus NEJM 2012

die PUNKTE
IHR AKTUELLES UND INNOVATIVES DIPLOMFORTBILDUNGSMAGAZIN
DFP LITERATUR
ENDOKRINOLOGIE 1/17
DFP-Beitrag publiziert im November 2017, gültig bis November 2020

Diagnose und Therapie des Hypoparathyreoidismus

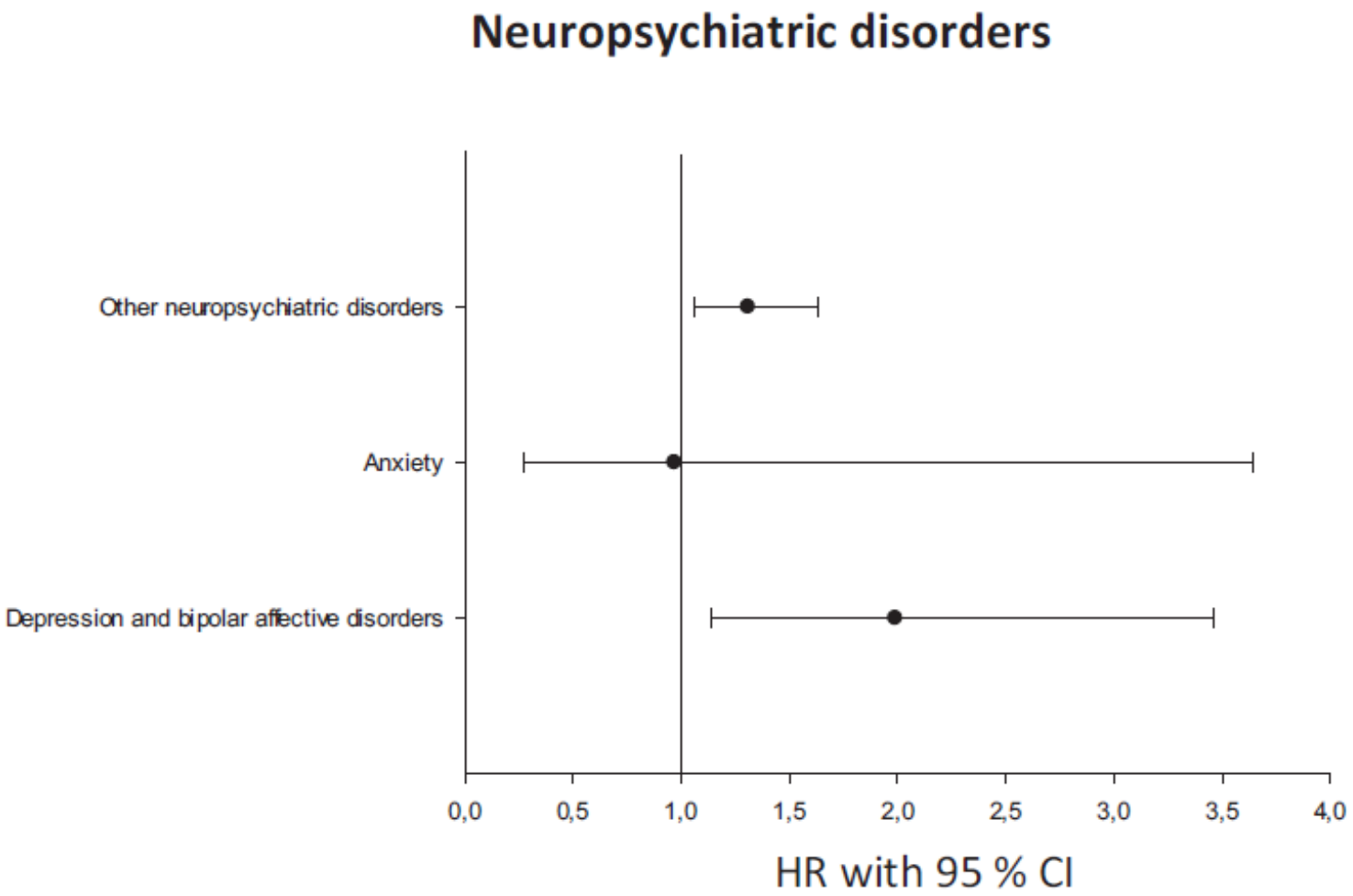
- Der chronische Hypoparathyreoidismus ist eine seltene endokrine Erkrankung, bei der vieles noch unklar ist, die aber seit einigen Jahren intensiver beforscht wird.
- In Österreich kann man mit ca. 2.500 Personen mit Hypoparathyreoidismus rechnen. Hauptursache ist das Fehlen des Parathormons (PTH) mit konsekutiver Hypokalzämie.
- Die derzeitige Standardtherapie ist rein symptomatisch und erfolgt vor allem durch die orale Gabe von Kalzium, aktivem und nativem Vitamin D. Zusätzlich können bei Bedarf Magnesium und Thiaziddiuretika eingesetzt werden.
- Aktuelle Studienergebnisse zum Thema PTH-Ersatz zeigen nunmehr vielversprechende Ergebnisse und könnten in Zukunft eine deutliche Verbesserung der Therapie und damit der Lebensqualität und Symptomkontrolle einleiten.

Autoren: cand. med. Maximilian Zach, assoz. Prof. Dr. Karin Amrein, MSc,
Klinische Abteilung für Endokrinologie und Diabetologie, Medizinische Universität Graz

2 PUNKTE

Tab. 2: Symptome und Langzeitkomplikationen des chronischen Hypoparathyreoidismus

Organsystem	Symptome, Manifestationen
Neuromuskulär	• Müdigkeit, Muskelschwäche • Tetanie, Muskelkrämpfe, neuromuskuläre Irritabilität • Laryngo- und/oder Bronchospasmus
Neurologisch, psychiatrisch	• Parästhesien (v. a. Finger/Zehen, perioral) • Brain Fog (verminderte Konzentrations- und Erinnerungsleistung) • Krampfanfälle • Bewegungsstörungen (Parkinsonismus, Chorea) • Depression, Angststörung • Basalganglienverkalkungen (Morbus Fahr)



Underbjerg L JBMR 2014

PRESSEMELDUNG
24 FEB 2017

- First hormone replacement therapy **for**

  THYROID disorder (...!)

- Orphan medicine Natpar recommended by CHMP for conditional marketing authorisation
- The European Medicines Agency (EMA) has recommended granting a conditional marketing authorisation in the European Union (EU) for **Natpar (parathyroid hormone).**

REPLACE – NATPAR-Zulassungsstudie

- 2009 bis 2011
- 33 Zentren, 8 Länder
- 134 Pat. , 2:1 Randomisierung
- **1-84 PTH** vs. Standardtherapie
- Prim. Endpunkt: > 50% weniger Ca/aktives Vitamin D mit ähnlichem Ca-Wert

Mannstadt M Lancet D&E 2015

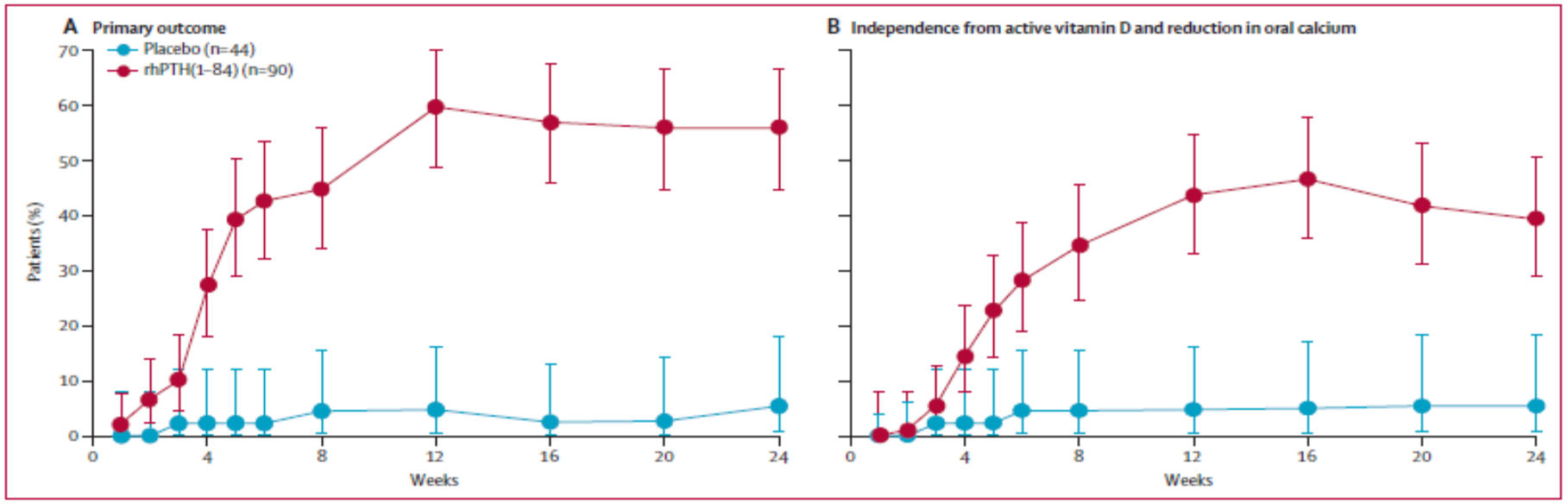


Figure 2: **Achievement of primary outcome and independence from active vitamin D and reduction in oral calcium during treatment period, according to patient diary data**
(A) Proportion of patients achieving the criteria for the primary endpoint throughout the 24 week treatment period. (B) Proportion of patients who were able to stop taking active vitamin D and to reduce their dose of oral calcium dose to ≤500 mg per day throughout the 24 week treatment period. rhPTH(1–84)= recombinant human parathyroid hormone 1–84.

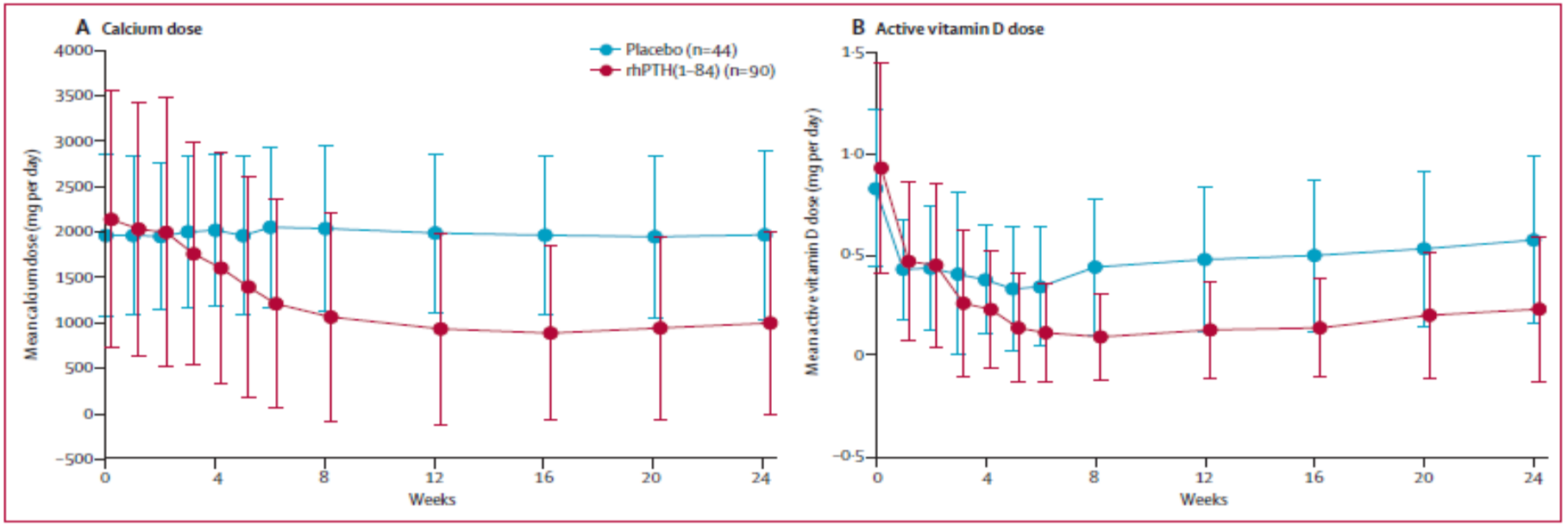


Figure 3: **Changes in calcium and active vitamin D doses throughout treatment period, by treatment group**
Mean oral calcium dose (A) and mean active vitamin D dose (B) in the placebo group and rhPTH(1–84) group throughout the 24 week treatment period. Error bars show SD. rhPTH(1–84)= recombinant human parathyroid hormone 1–84. From weeks 3–24, each mean measurement of calcium dose and active vitamin D dose differed significantly between groups (all $p<0.005$).

ENDOCRINE SOCIETY

Recombinant Human Parathyroid Hormone Effect on Health-Related Quality of Life in Adults With Chronic Hypoparathyroidism

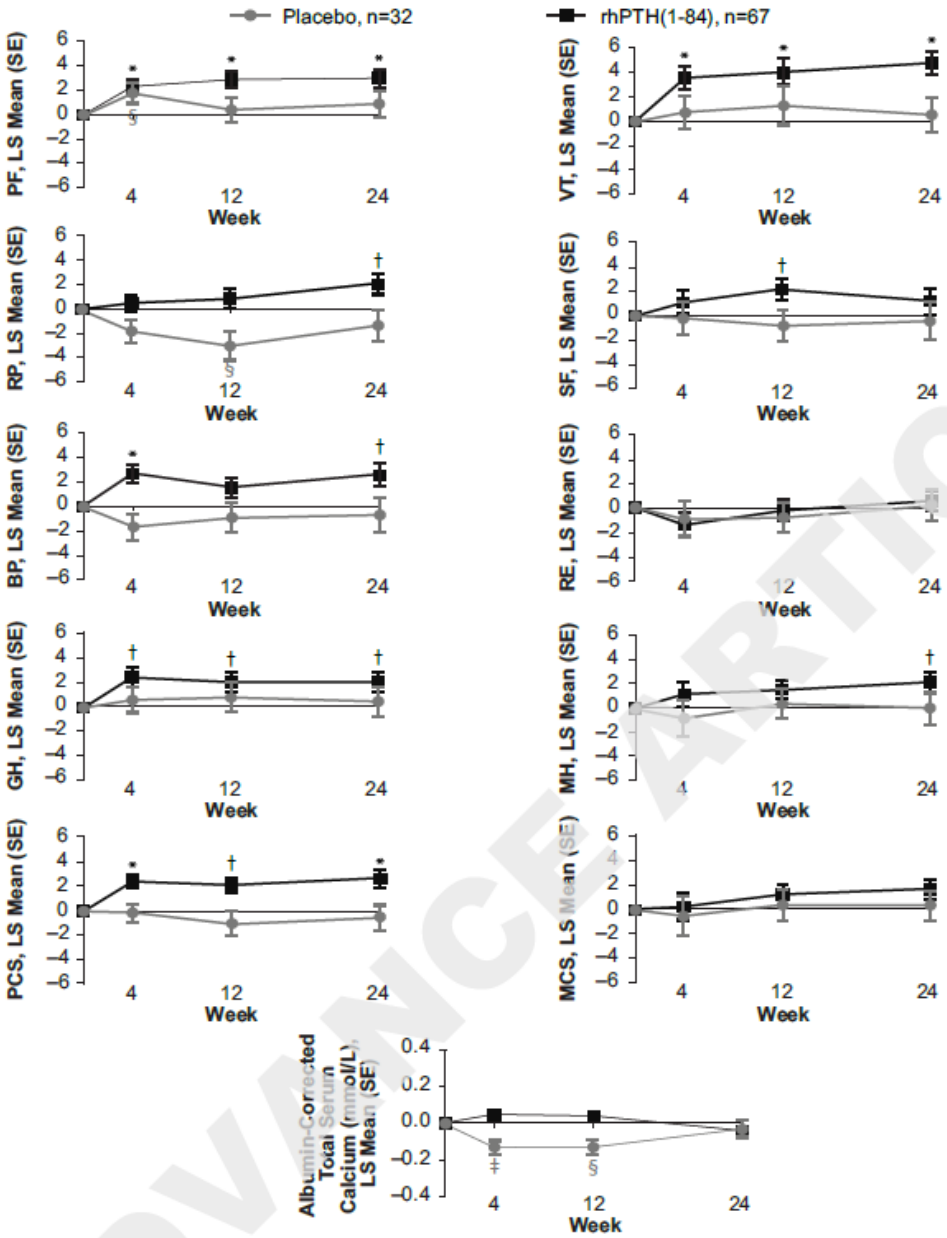
Tamara J. Vokes, Michael Mannstadt, Michael A. Levine, Bart L. Clarke, Peter Lakatos, Kristina Chen, Rebecca Piccolo, Alan Krasner, Dolores M. Shoback, John P. Bilezikian

The Journal of Clinical Endocrinology & Metabolism
Endocrine Society

Submitted: June 28, 2017
Accepted: October 27, 2017
First Online: November 01, 2017

***Patients*:** 122 adults with chronic hypoparathyroidism.
***Intervention(s)*:** Following an optimization period when calcium and/or active vitamin D supplements were adjusted to reach target serum calcium levels (8.0–9.0 mg/dL; 2.0–2.2 mmol/L), patients were randomized to receive placebo (n=39) or rhPTH(1-84) (n=83) (starting dose 50 μg/day, could be titrated up to 100 μg/day); supplement doses were adjusted to maintain target serum calcium levels.
***Main Outcome Measure(s)*:** Change from baseline (post-optimization, at randomization) to Week 24 in HRQoL as assessed by the SF-36v2 health survey.
***Results*:** Overall, the between-group differences were not statistically significant. However, in the rhPTH(1-84) group, there were significant improvements in the physical component summary score (P=0.004) and in body pain (P<0.05), general health (P<0.05), and vitality (P<0.001) domains as compared with baseline values. In the placebo group, there were no significant changes for any of the domains. The magnitude of change between 0 and 24 weeks in SF-36 scores was negatively correlated with baseline scores, such that patients with lower HRQoL at baseline were more likely to experience improvement in response to treatment.
***Conclusions*:** Treatment with rhPTH(1-84) may improve HRQoL in adults with hypoparathyroidism.

Vokes T JCEM 2017



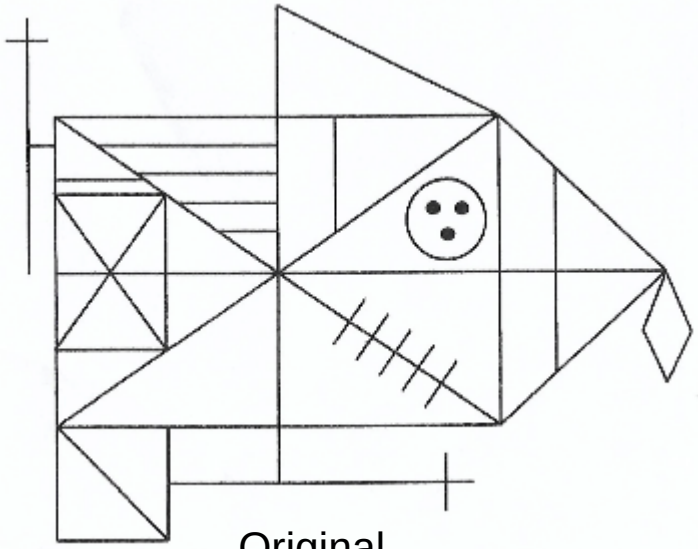
Vokes T JCEM 2017

Fall: Frau K.

- 54 J.
- 2012: Thyroidektomie (benigne Knotenstruma), postoperativ kein Serum-Ca^{2+} bestimmt (HypoCa^{2+}ämie)
- 2013: Fehltherapie f. 6 Monate (Calcitriol -> Vit.D)

- ehem. Köchin (60h/Woche), dzt. arbeitsunfähig
- Muskelschwäche (Gehstrecke <300m), Krämpfe, Gangunsicherheit, Parästhesien, „Brain Fog“

Rey-Osterrith Figure Test: visuelle Gedächtniseinschränkung



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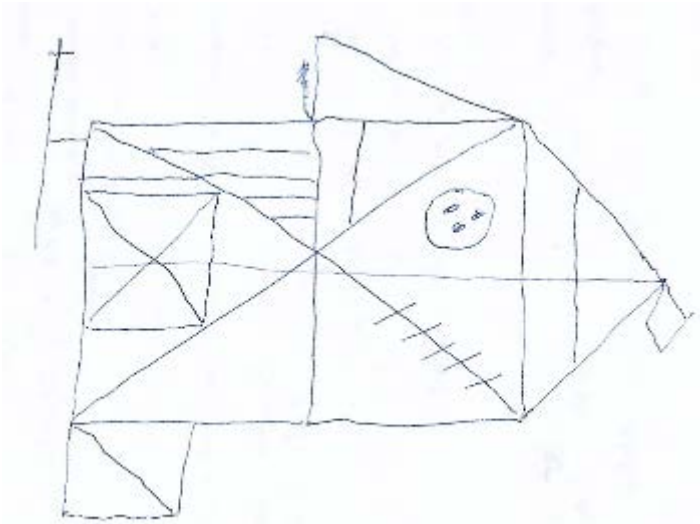
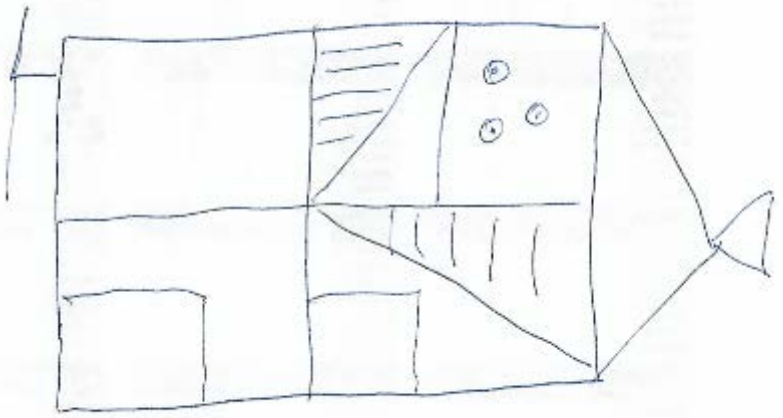


Abgezeichnet

nach 3 Min.



nach 30 Min.

- mehrfach Antrag auf Berufsunfähigkeitspension abgelehnt
- Empathy gap
- „Orphan disease“

THERAPIEZIELE

- **CALCIUM im unteren Normbereich oder darunter OHNE Hypokalzämiesymptome**
- **PHOSPHAT im Normbereich**
- **24h-HARNCALCIUM im Normbereich**
- **CA/PHOSPHAT-Produkt < 4.4 mml/l oder 55mg/dl**
- **MAGNESIUM im Normbereich**
- **VITAMIN D im Normbereich**

Bollerslev EJE 2016

HYPO- UND HYPERKALZÄMIE

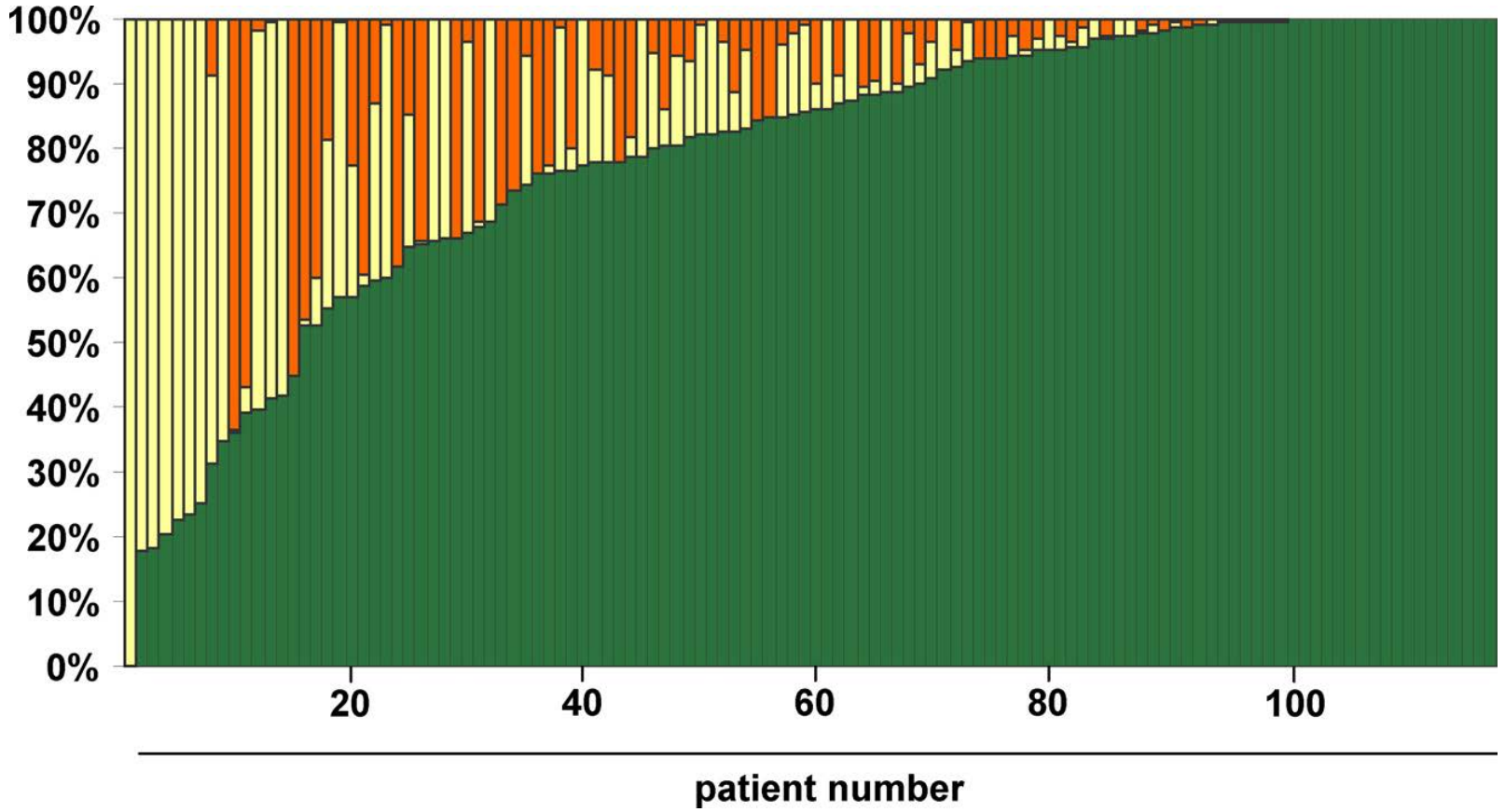


FIG. 2. Plot of proportion of observed time with serum calcium between 7.5 and 9.5 mg/dl (*green*), <7.5 mg/dl (*yellow*), or >9.5 mg/dl (*orange*). Each *column* represents one patient in the cohort.

Mitchell JCEM 2016

THERAPIE

- **ERSTLINIENTHERAPIE**
  - **CALCIUM und VITAMIN D AKTIV in geteilten Dosen**
- **VITAMIN D NATIV 400-800 IU**
- **Bei HYPERKALZIURIE: Einschränkung der Ca-Zufuhr (?), Na-eingeschränkte Diät, THIAZID**
- **MAGNESIUM**
- **PTH…???**

Table 2 Vitamin D metabolites in the management of chronic hypoparathyroidism[a].

Medication	Typical dose	Time to onset of action (days)	Time to offset of action (days)
Calcitriol ($1,25(OH)_2D_3$)	0.25–2.0 μg once or twice daily	1–2	2–3
Alfacalcidiol[b] ($1\alpha(OH)D_3$)	0.5–4 μg once daily	1–2	5–7
Dihydrotachysterol[b]	0.3–1.0 mg once daily	4–7	7–21
Vitamin D_2 (ergocalciferol) or vitamin D_3 (cholecalciferol)[c]	25 000–200 000 IU daily	10–14	14–75

[a]Derived from Shoback (4).
[b]Alfacalcidiol and dihydrotachysterol are rapidly activated in the liver to $1,25(OH)_2D$ and 25(OH) dihydrotachysterol.
[c]These compounds could be used in a setting where active vitamin D metabolites are not available and/or too expensive.

Bollerslev EJE 2016

Table 5. Indications for Considering the Use of rhPTH (1-84) in Hypoparathyroidism

1. Inadequate control of the serum calcium concentration (this could be due to intercurrent illness, compliance, absorption, or intrinsic changes in requirements that are beyond facile correction with calcium and active vitamin D)
2. Oral calcium/vitamin D medications required to control the serum calcium or symptoms that exceed 2.5 g of calcium or >1.5 μg of active vitamin D or >3.0 μg of the 1-α vitamin D analog
3. Hypercalciuria, renal stones, nephrocalcinosis, stone risk, or reduced creatinine clearance or eGFR (<60 mL/min)
4. Hyperphosphatemia and/or calcium-phosphate product that exceeds 55 mg^2/dL^2 (4.4 $mmol^2/L^2$)
5. A gastrointestinal tract disorder that is associated with malabsorption
6. Reduced quality of life

Brandi JCEM 2016

POSTOPERATIVER HYPOPARATHYREOIDISMUS

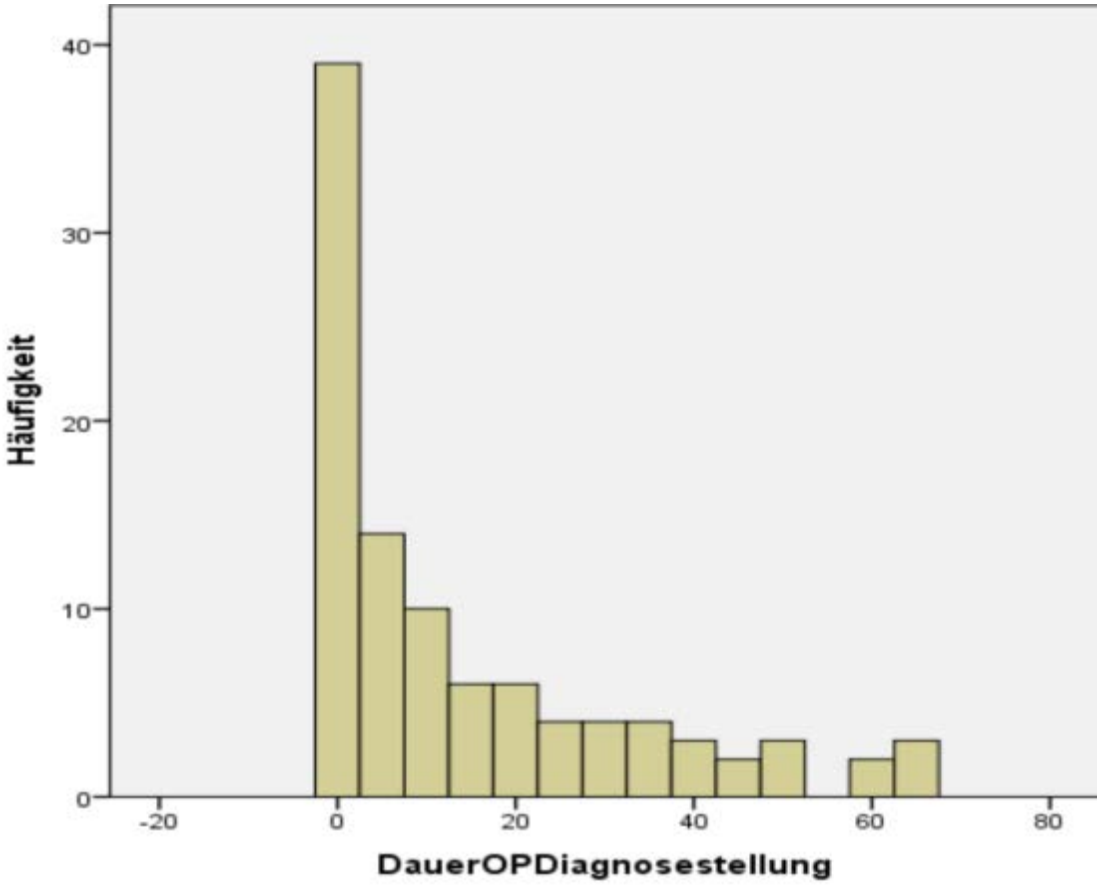
- Risiko bei Thyroidektomie: 0.2–4.5%*
- Prädisponierende Faktoren**:
  - Frauen
  - Grunderkrankung M. Basedow/Malignität
  - Totale Thyroidektomie, Re-OP
  - Probleme bei intraoperativer (Parathyreoidea) Identifizierung

* Asari R.: Arch Surg 2008, Thomus O.: Surgery 2003

** Thomusch O.: Surgery 2003, Dralle H.: Chirurg 2009, Testini M: Minerva Chir 2007

ZEITINTERVALL OP – DIAGNOSE

- Graz prospektiv (n=30): 1 Tag (1x 37 Jahre)
- Graz retrospektiv (n=100): 1. SD-OP bis Diagnose → 5,5a



POSTOPERATIVER HYPOPARATHYREOIDISMUS - GRAZ

- The average time from surgery to diagnosis of hypoparathyroidism was 13.9±17.6 years (range 0-67 years).
- Only a minority of patients was diagnosed
  - within the **first year after surgery** (n=32, **30.5%),**
  - 29 patients (**27.7%**) were diagnosed 2-10 years post surgery
  - 17 patients (**16.2%**) were diagnosed 10-20 years after surgery
  - 27 (**25.7%**) were diagnosed more than 20 years after surgery

Trummer, Amrein, submitted

NEUROKOGNITIVE ASPEKTE

Table 3 Comparison of raw scores (means ± S.D.) and frequency of impaired neurocognitive tests in the patient and control groups.

Test	Hypoparathyroid ($n=62$)	Controls ($n=70$)	*P*	*P**
Global Cognitive Dysfunction Score				
Raw score	4.6 ± 3.36	2.2 ± 2.58	0.000005	< 0.001
% Impaired (≥ 6)	32.3%	5.7%	0.00008	0.001
Verbal Adult Intelligence Scale (VQ)				
Raw score	88.4 ± 11.94	92.4 ± 8.23	0.0275	0.36
% Impaired (VQ < 80)	29.0%	8.6%	0.002	0.03
Hindi Mental State Examination				
Raw score	26.4 ± 3.26	27.2 ± 2.09	0.31	0.99
% Impaired (score < 24)	17.7%	5.7%	0.03	0.39
Brief Psychiatric Rating Scale				
Raw score	25.5 ± 5.66	20.3 ± 2.72	$< 10^{-8}$	< 0.001
% Impaired (score > 22)	66.1%	24.3%	0.0000013	< 0.001
Trail Making Test (A)				
Raw score (s)	61.9 ± 47.43	40.6 ± 22.89	0.00053	< 0.01
% Impaired (time taken ≥ 45 s)	56.4%	25.7%	0.0003	< 0.01
Trail Making Test (B)				
Raw score (s)	126.0 ± 74.01	88.2 ± 50.47	0.0004	< 0.01
% Impaired (with time taken ≥ 102 s)	45.2%	25.7%	0.019	0.25
Abnormal Involuntary Movement Scale				
% Impaired (score ≥ 2)	9.7%	0.0%	0.008	0.10
Benton Visual Retention Test				

Aggarwal 2015

NEUROKOGNITIVE ASPEKTE

Abnormal Involuntary Movement Scale				
% Impaired (score $\geq$2)	9.7%	0.0%	0.008	0.10
Benton Visual Retention Test				
Raw score	9.9$\pm$5.03	5.4$\pm$2.97	$<10^{-7}$	$<$0.001
% Impaired (no. of errors $\geq$8)	62.9%	25.7%	0.000017	$<$0.01
Stroop Word				
Raw score (no. of correct words read)	53.9$\pm$21.87	67.0$\pm$22.67	0.00097	0.01
% Impaired (score $<$50)	48.4%	24.3%	0.0039	0.05
Stroop Colour				
Raw score (no. of correct colours read)	45.0$\pm$16.81	50.8$\pm$17.55	0.08	0.99
% Impaired (score $<$34)	22.6%	17.1%	0.43	0.99
Stroop Colour–Word Combination				
Raw score (no. of correct word–colours read)	27.7$\pm$13.44	35.4$\pm$16.09	0.0036	0.05
% Impaired (score $<$19)	22.6%	10.0%	0.0486	0.63
Bender Gestalt Test				
Raw score (total no. of weighted errors)	4.4$\pm$3.93	2.2$\pm$2.47	0.0007	$<$0.01
% Impaired (score $\geq$3)	61.3%	32.9%	0.0011	0.01
Finger Tapping Test				
Raw score (no. of correct patterns)	3.7$\pm$1.81	4.6$\pm$1.33	0.004	0.05
% Impaired (score $<$4)	38.7%	21.4%	0.03	0.39
PGI-Memory scale Total	71.0$\pm$11.37	76.6$\pm$8.53	0.0013	0.02
% Impaired (score $<$72)	46.8%	25.7%	0.012	0.16
SF-36-PCS	44.8$\pm$9.49	52.6$\pm$7.90	0.000001	$<$0.001
SF-36-MCS	43.3$\pm$10.26	45.8$\pm$8.75	0.25	0.99

*P values corrected for multiple testing. VQ, verbal quotient.

Aggarwal 2015

Agha et al. BMC Surgery (2016) 16:51
DOI 10.1186/s12893-016-0165-y

BMC Surgery

CASE REPORT Open Access

Living-donor parathyroid allotransplantation for therapy-refractory postsurgical persistent hypoparathyroidism in a nontransplant recipient – three year results: a case report

Ayman Agha[1*], Marcus Nils Scherer[1], Christian Moser[1], Thomas Karrasch[3], Christiane Girlich[2], Fabian Eder[4], Ernst-Michael Jung[5], Hans Juergen Schlitt[1] and Andreas Schaeffler[3]

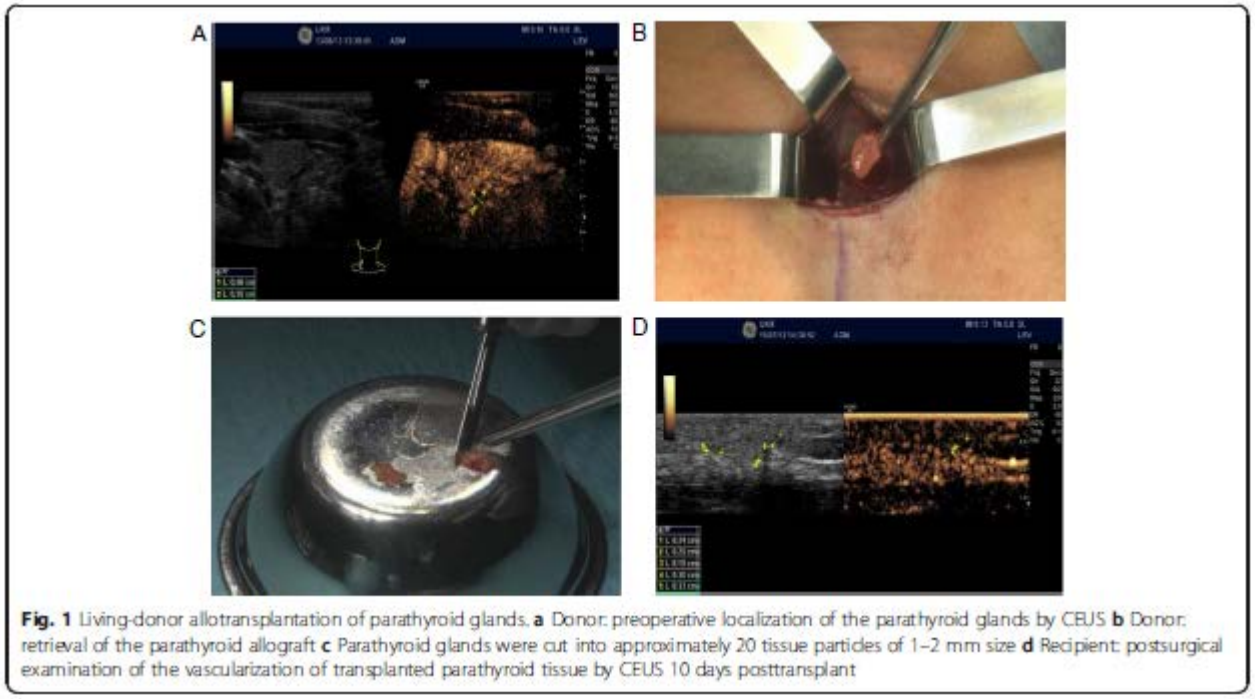


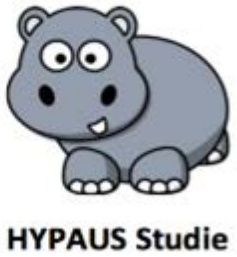
Fig. 1 Living-donor allotransplantation of parathyroid glands. **a** Donor: preoperative localization of the parathyroid glands by CEUS **b** Donor: retrieval of the parathyroid allograft **c** Parathyroid glands were cut into approximately 20 tissue particles of 1–2 mm size **d** Recipient: postsurgical examination of the vascularization of transplanted parathyroid tissue by CEUS 10 days posttransplant

DIE HYPAUS-STUDIE

Prospektive Hypoparathyreoidismus-Kohorte

1. Analyse

Karin Amrein, Maximilian Zach



DIE STUDIE:

- Start: Jänner 2017
- Prospektive multizentrische Kohortenstudie

- Schilddrüsen Institut Buchinger
- Med. Universität Graz, Wien, Innsbruck
- SchilddrüsenIEndokrinologieIOsteoporose Institut Dobnig
- Schilddrüsenpraxis Lehner, Linz und Wels

ABLAUF:

- Routinekontrolle
- Fragebogenuntersuchung
- Ätiologie, Symptome, Therapie, Komplikationen, Folgeerkrankungen, Lebensqualität (QoL)
- Datenbank: Phoenix

- Neurokognitive und -psychiatrische Testung optional (Univ.-Klinik f. Psychiatrie Graz)

DEMOGRAFIE

- Datensammlungszeitraum: Jänner – Oktober 2017
- 30 ProbandInnen
  - MedUni Graz: 19
  - MedUni Innsbruck: 8
  - SD-Praxis Dr. Lehner (Wels): 3

  - 21♀ u. 9♂ (70 vs. 30%)
  - Alters-Ø: 50a

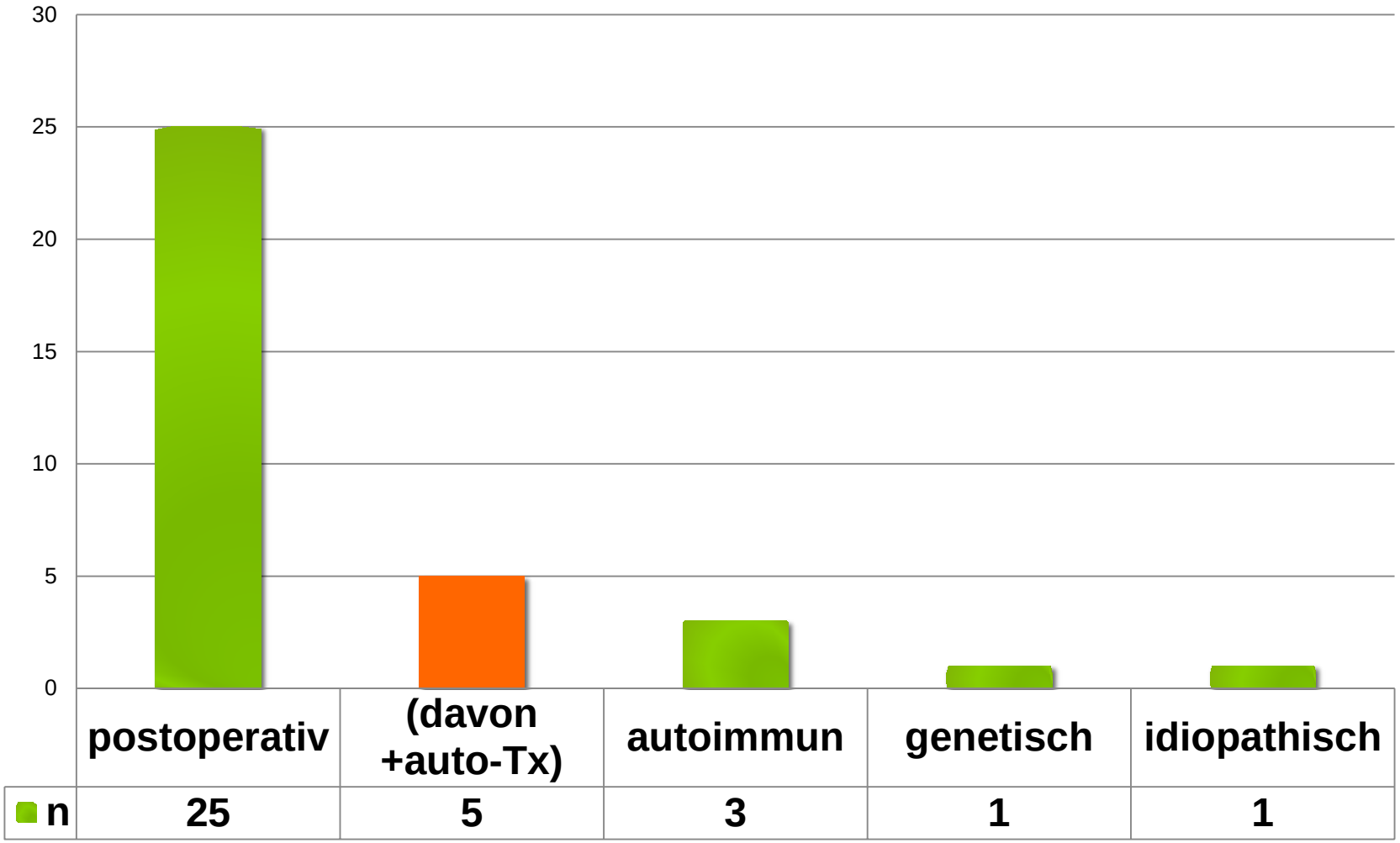
→ „...Hypoparathyreoidismus tritt zu 70-80% bei Frauen auf...“[1]

  - Alter bei Diagnose (median): 45,5a
    - Min: 5a Max: 68a

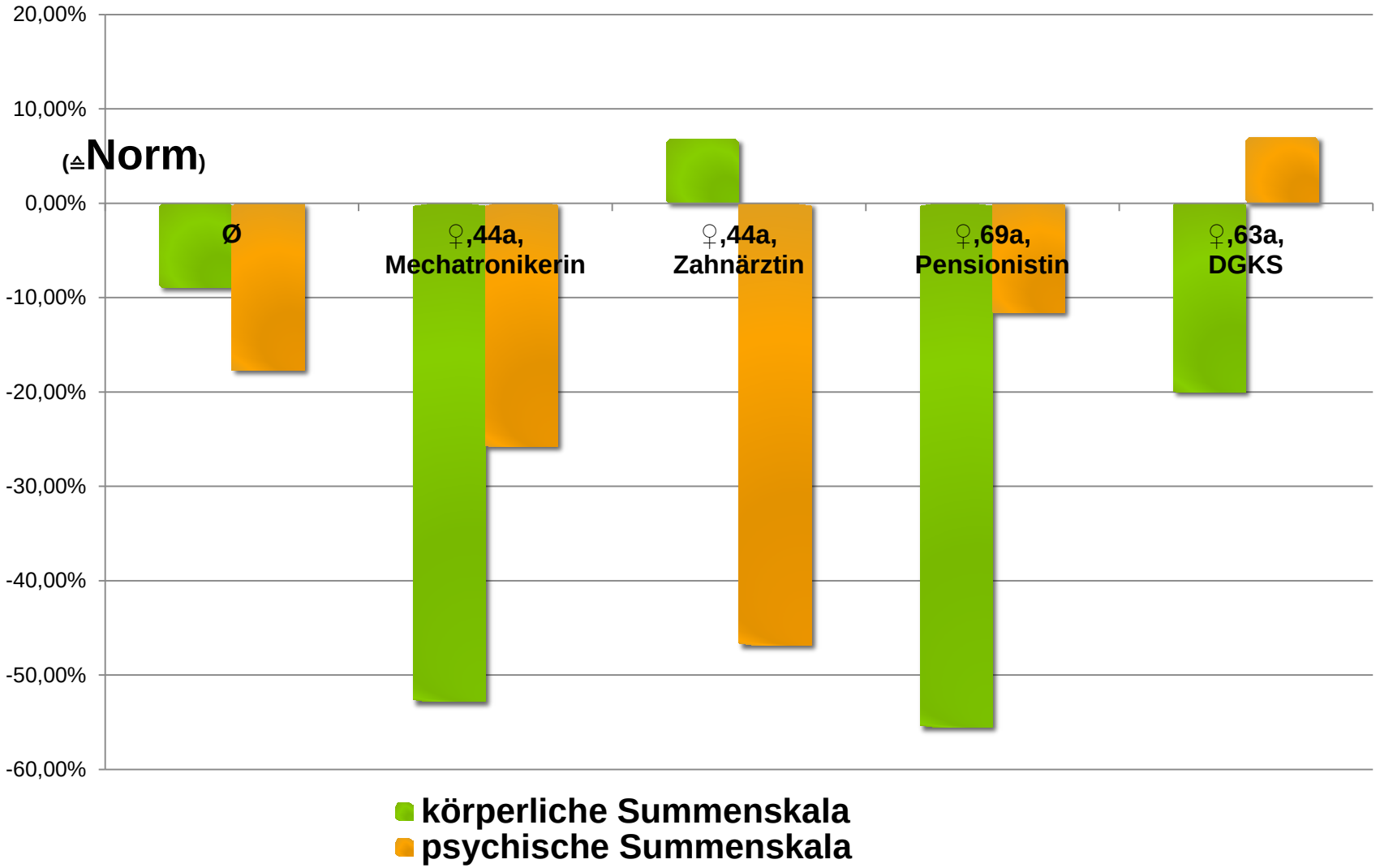
  - Erkrankungsdauer (Ø): 8,5a

([1] Bilezikian JP, Khan A, Potts JT, Jr., Brandi ML, Clarke BL, Shoback D, et al. Hypoparathyroidism in the adult: epidemiology, diagnosis, pathophysiology, target-organ involvement, treatment, and challenges for future research. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research. 2011;26(10):2317-37.

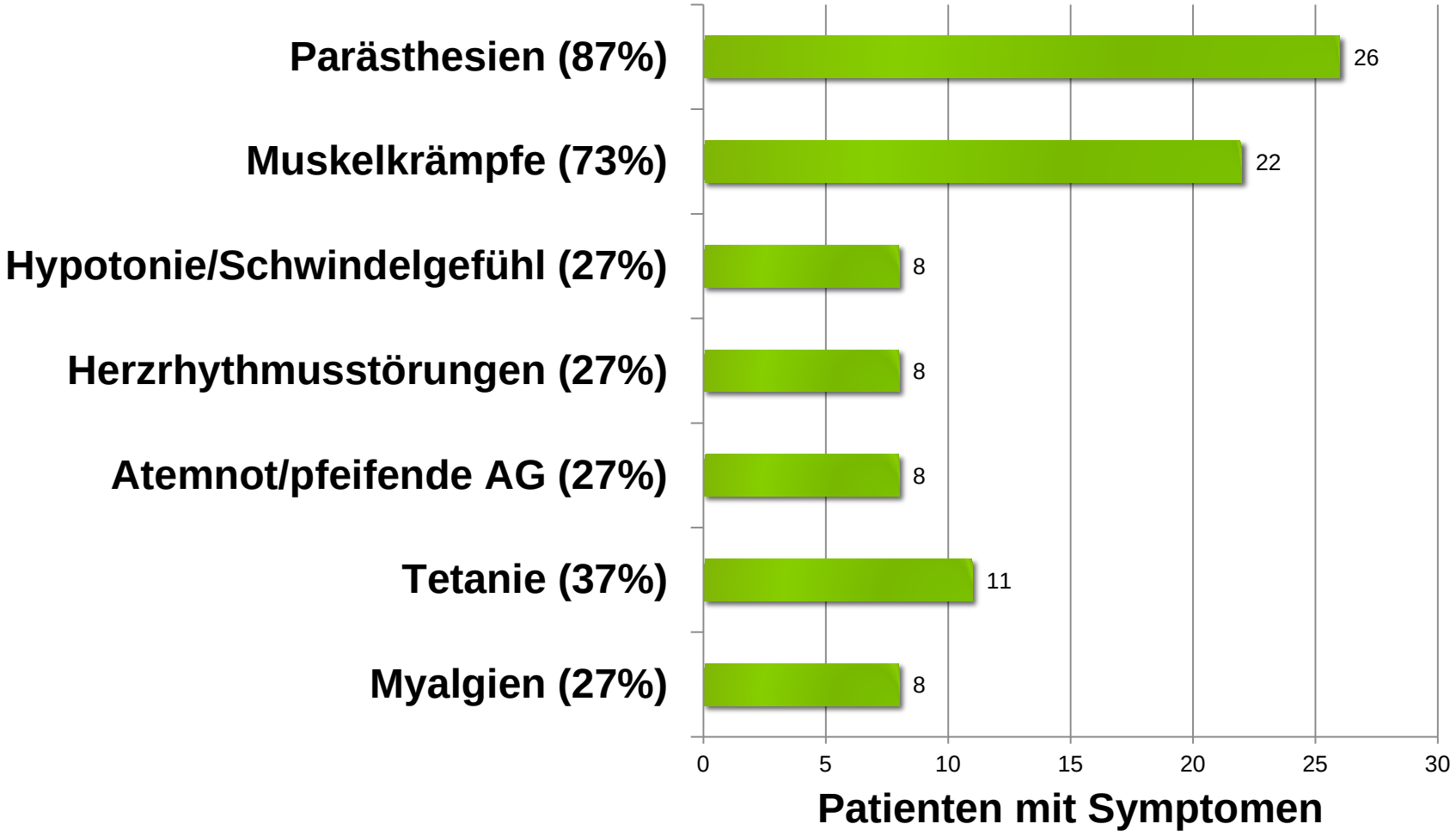
ÄTIOLOGIE


30
25
20
15
10
5
0
postoperativ
(davon +auto-Tx)
autoimmun
genetisch
idiopathisch
n
25
5
3
1
1

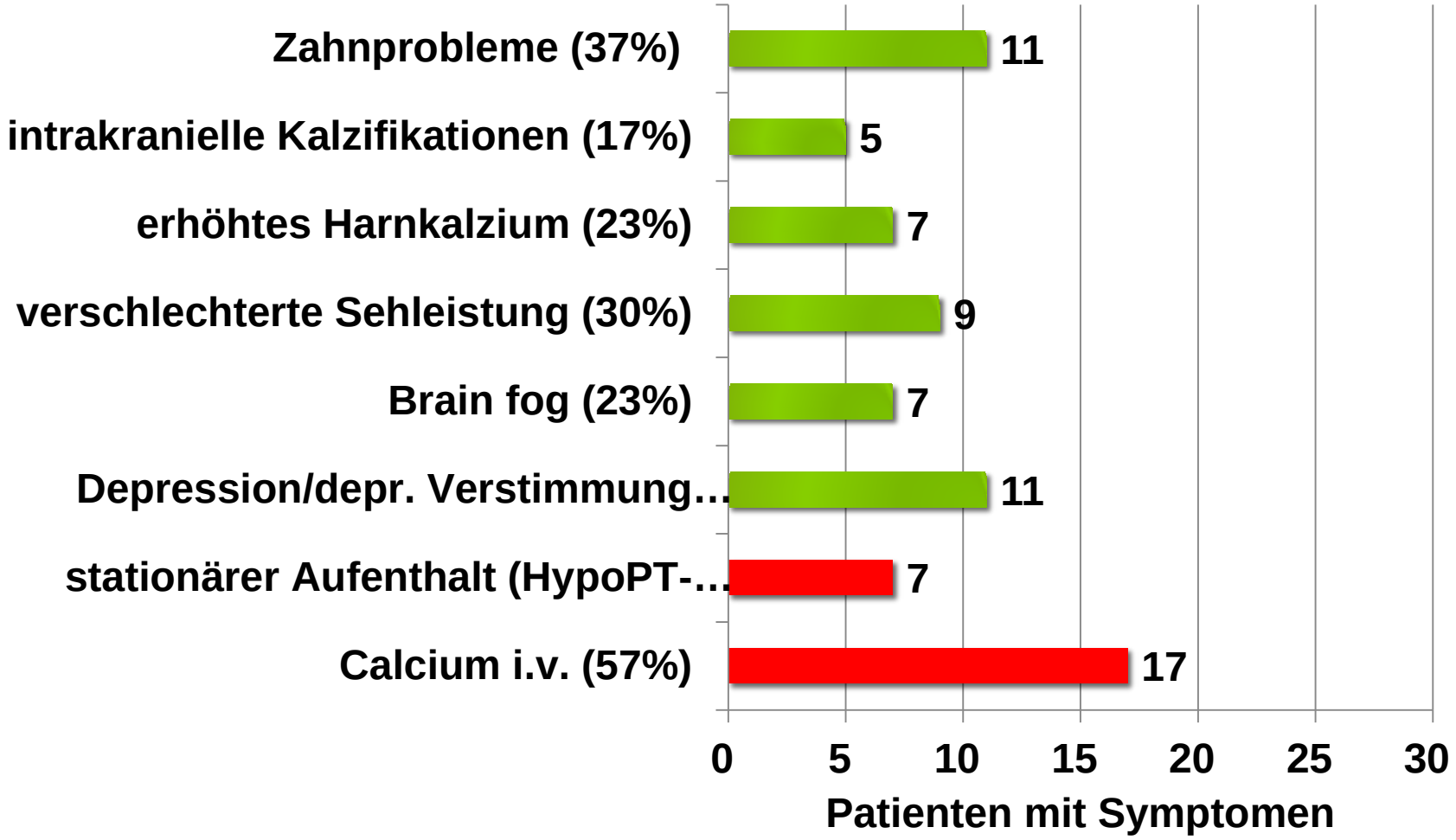
QOL SF-12 (VERGLEICH STEIRISCHES NORMKOLLEKTIV)



SYMPTOME (1)


Parästhesien (87%)
26
Muskelkrämpfe (73%)
22
Hypotonie/Schwindelgefühl (27%)
8
Herzrhythmusstörungen (27%)
8
Atemnot/pfeifende AG (27%)
8
Tetanie (37%)
11
Myalgien (27%)
8
0
5
10
15
20
25
30
Patienten mit Symptomen

SYMPTOME (2)


Zahnprobleme (37%)
11
intrakranielle Kalzifikationen (17%)
5
erhöhtes Harnkalzium (23%)
7
verschlechterte Sehleistung (30%)
9
Brain fog (23%)
7
Depression/depr. Verstimmung…
11
stationärer Aufenthalt (HypoPT-…
7
Calcium i.v. (57%)
17
0
5
10
15
20
25
30
Patienten mit Symptomen

AUSBLICK – OFFENE FRAGEN

- Mehr prospektive Daten
  - Lebensqualität!?
  - Neuropsychiatrische Symptome
  - Neurokognitive Funktionen
- Alternative Behandlungsmöglichkeiten
  - Parathormon (1-84 in USA seit 02/15 zugelassen, EU Zulassung 2017-Kosten… Krankenkassen…)
  - Teriparatid off-label; Pumpe, Tbl?, Tx?, Ca-Heimmessung? …