Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

und

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2023-B-110 Palopegteriparatid

Stand: Juli 2023

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Palopegteriparatid

[zur Behandlung von Hypoparathyreoidismus bei Erwachsenen]

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	*siehe Übersicht II*: Zugelassene Arzneimittel im Anwendungsgebiet
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Zugelassene Ausnahmen zum gesetzlichen Verordnungsausschluss nach § 34 Absatz 1 Satz 2 SGB V (OTC-Übersicht) nach Anlage I der AM-RL für: - 12. Calciumverbindungen als Monopräparate nur bei Pseudohypo- und Hypoparathyreodismus.
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche*

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Palopegteriparatid	<u>Anwendungsgebiet laut Beratungsanforderung:</u> „Palopegteriparatid ist eine PTH-Ersatztherapie für die Behandlung von Hypoparathyreoidismus bei Erwachsenen.“
Nebenschilddrüsenhormone	
Paratthyroid-hormon H05AA03 Natpar®	Natpar ist als Zusatztherapie bei erwachsenen Patienten mit chronischem Hypoparathyreoidismus angezeigt, deren Erkrankung sich durch die Standardtherapie allein nicht hinreichend kontrollieren lässt.
Calcium	
Calciumchlorid B05XA07 Calciumchlorid 5,5% Baxter	Calciummangelzustände, insbesondere bei hypochlorämischer alkalotischer Stoffwechsellage.
Calciumcitrat A12AA13 Calcium DU-Pharma 200 mg Filmtabletten	Zur Vorbeugung eines Calciummangels bei erhöhtem Bedarf. Zur unterstützenden Behandlung der Osteoporose.
Calciumcarbonat A12AA04 Calcium-dura 600 mg Filmtabletten	Zur Vorbeugung eines Calciummangels bei erhöhtem Bedarf bei Erwachsenen. Zur unterstutzenden Behandlung der Osteoporose.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Calciumgluconat B05B B01 Calciumgluconat B. Braun 10 % Injektionslosung	Behandlung einer akuten symptomatischen Hypocalcämie.
Calcium (Calcium-D-gluconat – Calciumlactat (2:3) 2 H_2O und Calciumcarbonat) A12AA20 Calcium-Sandoz® Forte 500 mg	- zur Vorbeugung eines Calciummangels bei Erwachsenen, wenn eine ausreichende Calciumversorgung mit der Nahrung nicht erreicht wird - Behandlung eines Calciummangels bei Kindern ab 6 Jahren, Jugendlichen und Erwachsenen
Vitamin-D und Analoga	
Calcitriol A11CC04 Decostriol®	Hypoparathyreoidismus (Unterfunktion der Nebenschilddruse) - postoperativer Hypoparathyreoidismus - idiopathischer Hypoparathyreoidismus - Pseudohypoparathyreoidismus (zur Sicherung der Diagnose kann die Bestimmung des Parathormons herangezogen werden)
Alfacalcidol A11CC03 Tevacidol®	Bei Hypoparathyreoidismus oder hypophosphatämischer (Vitamin D-resistenter) Rachitis/Osteomalazie kann eine Zusatztherapie mit Tevacidol dann indiziert sein, wenn ein Calcium-Plasmaspiegel kleiner als 2,2 mmol/l vorliegt.
Dihydrotachysterol[1] A11CC02	Hypoparathyreoidismus (idiopathisch und postoperativ), Pseudohypoparathyreoidismus.

[1] nicht in Deutschland verfügbar

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Atiten Lösung	

Quellen: AMIce-Datenbank, Fachinformationen, Stand Juli 2023

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2023-B-110 (Palopegteriparatid)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	13. Juni 2023

Inhaltsverzeichnis

Abkürzungsverzeichnis

ADH	Autosomal Dominant Hypocalcemia
APS-1	Autoimmune Polyendocrine Syndrome Type 1
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BMD	Bone Mineral Density
CaSR	Calcium-Sensing Receptor
eGFR	Estimated Glomerular Filtration Rate
FDA	Food and Drug Administration
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HR	Hazard Ratio
hPTH	Human PTH
HRpQCT	High Resolution Peripheral Quantitative Computed Tomography
HypoPT	Hypoparathyroidism
ICTRP	World Health Organization International Clinical Trials Registry Platform
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LoE	Level of Evidence
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
PTH	Parathyroid Hormone
rhPTH	Recombinant Human PTH
RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Behandlung von Hypoparathyreoidismus bei Erwachsenen

Hinweis zur Synopse: „Informationen hinsichtlich nicht zugelassener Therapieoptionen sind über die vollumfängliche Darstellung der Leitlinienempfehlungen dargestellt“.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur *Hypoparathyreoidismus* durchgeführt und nach PRISMA-S dokumentiert [A]. Die Recherchestrategie wurde vor der Ausführung anhand der PRESS-Checkliste begutachtet [B]. Es erfolgte eine Datenbankrecherche ohne Sprachrestriktion in: The Cochrane Library (Cochrane Database of Systematic Reviews), PubMed. Die Recherche nach grauer Literatur umfasste eine gezielte, iterative Handsuche auf den Internetseiten von Leitlinienorganisationen. Ergänzend wurde eine freie Internetsuche (https://www.google.com/) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Der Suchzeitraum wurde auf die letzten fünf Jahre eingeschränkt und die Recherche am 08.05.2023 abgeschlossen. Die detaillierte Darstellung der Recherchestrategie inkl. verwendeter Suchfilter sowie eine Angabe durchsuchter Leitlinienorganisationen ist am Ende der Synopse aufgeführt. Mit Hilfe von EndNote wurden Dubletten identifiziert und entfernt. Die Recherche ergab 151 Referenzen.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Referenzen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt 4 Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Edafe O et al., 2019 [1].

Calcium, vitamin D or recombinant parathyroid hormone for managing post-thyroidectomy hypoparathyroidism

Fragestellung

[…] to assess the effects of calcium, vitamin D and recombinant parathyroid hormone in managing post-thyroidectomy hypoparathyroidism.

Methodik

Population:

- People who developed hypoparathyroidism following thyroidectomy

Intervention/Komparator:

- Oral calcium or vitamin D supplements versus placebo.
- Oral calcium plus vitamin D versus oral calcium plus placebo.
- Recombinant parathyroid hormone (1-84 or 1-34) plus oral calcium plus vitamin D versus placebo plus oral calcium plus vitamin D.

Endpunkte:

Primary outcomes

- Health-related quality of life.
- Long-term hypoparathyroidism.
- Adverse events.

Secondary outcomes

- All-cause mortality.
- Occurrence of epilepsy.
- Hypercalcaemia.
- Socioeconomic effects.

Recherche/Suchzeitraum:

- Randomised controlled trials (RCTs) and controlled clinical trials:
  - CENTRAL, MEDLINE, PubMed, Embase as well as ICTRP Search Portal and ClinicalTrials.gov
  - We aimed to identify other potentially eligible trials or ancillary publications by searching the reference lists of included studies, systematic reviews, meta-analyses and health technology assessment reports.
  - The date of the last search for all databases was 17 December 2018 (except Embase, which was last searched on 21 December 2017).

Qualitätsbewertung der Studien:

- Cochrane 'Risk of bias' assessment tool

Ergebnisse

Anzahl eingeschlossener Studien:

- No study was eligible for inclusion in the systematic review.
- Results of the search:

  We screened a total of 1751 records. Twenty-nine full text articles (involving 25 studies) were retrieved following title and abstract screen. None met our inclusion criteria as specified in the protocol. We did not identify any ongoing trials.

Fazit der Autoren

Findings highlighted deficiencies in the current literature in the management of post-thyroidectomy hypocalcaemia. Randomised controlled trials (RCTs) evaluating the use of calcium, vitamin D and PTH in post-thyroidectomy hypocalcaemia are needed. […]

3.2 Systematische Reviews

Es wurden keine relevanten Systematischen Reviews identifiziert.

3.3 Leitlinien

Khan AA et al., 2022 [2].

Management of Hypoparathyroidism

Zielsetzung

[…] an evidence-based approach to the management of Hypoparathyroidism (HypoPT)

Methodik

Methodikeranmerkung: Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund fehlender höherwertiger Evidenz wird die LL ergänzend dargestellt.

Grundlage der Leitlinie

- Repräsentatives Gremium – unklar: Hintergrund der Autorenschaft nicht identifiziert, Patientenvertretung wurde eingebunden, Ausmaß jedoch unklar;
- Interessenkonflikte dargelegt und finanzielle Unabhängigkeit nicht vorliegend: “We acknowledge unrestricted financial support from: Amolyt, Ascendis, Calcilytix and Takeda. They had no input into the planning or design of the project, the conduct of the reviews, evaluation of the data, writing or review of the manuscript, its content, conclusions, or recommendations contained herein.”;
- Systematische Suche, Auswahl und Bewertung der Evidenz: Systematische Suche indirekt durch Bezugnahme auf einen systematischen Review von Yao et al., 2022 [4] und einen Systematic Current Practice Review (von van Uum et al., 2022), systematische Auswahl und Bewertung der Evidenz sind im Rahmen dieser Publikationen beschrieben; Eigenständige systematische Suche, Auswahl und Bewertung der Evidenz im Rahmen der LL sind nur vage beschrieben und mit größeren Unsicherheiten verbunden;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt: formale Konsensusprozesse für „Graded Recommendations“ teilweise dargelegt, Unklarheiten (bspw. zu konkreten Abstimmungsprozessen, Empfehlungen bei Dissens, etc.) verbleiben; größere Unklarheiten zu „Ungraded Recommendations“; externes Begutachtungsverfahren nur in Form des Peer Reviews durch das „Journal of Bone and Mineral Research“ ersichtlich;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt - trifft teilweise zu: Empfehlungen sind eindeutig, die Verbindung zu der zugrundeliegenden Evidenz ist jedoch nicht direkt ersichtlich;
- Regelmäßige Überprüfung der Aktualität nicht identifiziert.

Referenzen

van Uum S, Shrayyef M, M’Hiri I, et al. Initial assessment and monitoring of patients with chronic hypoparathyroidism: a systematic current practice survey. J Bone Miner Res. 2022. https://doi.org/10.1002/jbmr.4698.

Yao L, Li J, Li M, et al. Parathyroid hormone therapy for managing chronic hypoparathyroidism: a systematic review and meta-analysis. J Bone Miner Res. 2022. https://doi.org/10.1002/jbmr.4676.

Recherche/Suchzeitraum:

Siehe „Methodik: Systematische Suche, Auswahl und Bewertung der Evidenz“: „Eigenständige systematische Suche, Auswahl und Bewertung der Evidenz im Rahmen der LL sind nur vage beschrieben und mit größeren Unsicherheiten verbunden.“

- Yao et al., 2022 [4]:

  Relying in part on a prior review, we searched Embase, PubMed, and Cochrane CENTRAL from inception to May 2022 using key words hypoparathyroidism, hypocalcemia, hypocal*, hypoPT, parathyroid hormone, PTH, rhPTH, PTH(1–34), teriparatide, PTH(1–84), TransCon PTH, and random*.

LoE/GoR

- Graded recommendations:

  Graded recommendations followed a structured process that included framing questions in patient/intervention/comparator/outcome format; conduct of a systematic evidence search and associated summary as described in the previous paragraph; specification of values and preferences; and classifying and presenting recommendations as strong or weak with the corresponding quality of evidence.

  ➔ LoE: strong or weak with the corresponding quality of evidence

- Ungraded recommendations:

  Ungraded recommendations involved none of these structured approaches and are presented as descriptions of the practice of the panelists in managing patients with HypoPT. Ungraded recommendations are presented as “we propose.” The intent was to achieve consensus on all recommendations. There was no provision for voting.

  ➔ LoE: keine strukturierte Bewertung von Evidenz

Empfehlungen

Graded Recommendations

1. In patients with chronic hypoparathyroidism (HypoPT), the panel suggests conventional therapy as first line therapy rather than administration of parathyroid hormone (PTH) (weak recommendation, low quality evidence).

   Comment - When conventional therapy is deemed unsatisfactory the panel considers use of PTH.

Ungraded Recommendations

In patients with HypoPT, the panel proposes:

1.1. Treat with calcium and active vitamin D analogue therapy, with a goal to raise serum calcium (albumin adjusted or ionized) into the target range; ie, the lower half of the normal reference range or just below the normal reference range. At this time, it is not clear how to best balance the doses of calcium and active vitamin D analogue therapy.

1.2. Alleviate symptomatic hypocalcemia while avoiding hypercalcemia.

1.3. Avoid hypercalciuria when titrating calcium and active vitamin D analogue therapy, aiming for low normal plasma calcium levels. The panel proposes achieving a 24-hour urinary calcium level <6.25/7.5 mmol/24 hours (250/300 mg/24 hours) for adult women and men, respectively. Data from the general population has shown a relationship between hypercalciuria and the development of renal stones—such data does not exist in patients with HypoPT; however, panel members infer that hypercalciuria may be associated with a higher risk of renal stones in patients with HypoPT as well and thus seek to avoid hypercalciuria.

1.4. Avoid hyperphosphatemia. Panel members prescribe calcium supplements with meals to serve as phosphate binders, implement a low phosphate diet in adults and judiciously use active vitamin D analogue therapy. No data are available on the use of other types of phosphate binders in HypoPT. Hyperphosphatemia may be associated with an increased incidence of ectopic calcification; however, currently there is no evidence of this in HypoPT.

1.5. Treat to normalize plasma magnesium levels. Magnesium supplements can be used as tolerated by the patient.

1.6. Aim to achieve a 25-hydroxyvitamin D level in the normal reference range.

1.7. Consider treating hypercalciuria with thiazide diuretics in conjunction with a low sodium diet with careful monitoring of serum magnesium, potassium, and renal function.

1.8. Consider PTH replacement therapy in patients who are not adequately controlled on conventional therapy. Inadequate control is considered to be any one of the following: (i) symptomatic hypocalcemia; (ii) hyperphosphatemia; (iii) renal insufficiency; (iv) hypercalciuria; (v) poor quality of life.

1.9. Individuals with poor compliance, malabsorption or who are intolerant of large doses of calcium and active vitamin D may also benefit from PTH therapy.

Methodikeranmerkung: Die gesonderten Empfehlungen für Schwangere und Stillende 2.1-2.5 können der Original-LL entnommen werden.

Hintergrund

Conventional Therapy

In addition to a calcium-rich diet, the conventional therapy for patients with HypoPT includes calcium supplementation and active vitamin D analogue therapy (calcitriol, alfacalcidol, or dihydrotachysterol) in varying doses.(1–4) Doses are titrated to obtain serum calcium levels in the lower half or slightly below the reference interval.

Oral calcium preparations contain varying amounts of elemental calcium: calcium carbonate (40% elemental calcium), calcium citrate (21%), calcium gluconate (9%), and calcium lactate (13%). Calcium salts are absorbed well(12,13) and also act as phosphate binders to lower serum phosphorus when given with meals.(13) If calcium carbonate is used, it should be taken with a meal for enhanced absorption. The absorption of calcium in the form of calcium citrate is not affected by food intake.(14)

The limitations of current conventional therapy include a significant pill burden with complicated regimens, fluctuations in serum calcium, and diminished QoL. Active vitamin D increases the absorption of calcium and phosphorus in the small bowel.(15) This increases serum calcium and can also result in increased renal filtered calcium load with further elevations in urinary calcium as well as elevations in serum phosphorus. Hypercalciuria and renal calcification appear to be common complications of long-term conventional therapy. Currently, however, we have not been able to clearly document a correlation between hypercalciuria and the development of kidney stones or renal impairment in patients with HypoPT.(16–18)

It is recommended to monitor serum phosphorus and urine calcium and aim to normalize both of these parameters in patients on conventional therapy.(1,5) This may require reductions in the doses of calcium and active vitamin D.(19) Patients with nonsurgical HypoPT due to an activating mutation in the calcium sensing receptor (ie, autosomal dominant hypocalcemia [ADH]) are more likely to develop hypercalciuria in response to calcium supplements.(20)

PTH Therapy

Replacement therapy with intact recombinant human PTH (1-84) [rhPTH (1-84)] has been approved as an adjunct to conventional therapy by regulatory agencies. In addition, effects of therapy with PTH (1-34) in HypoPT in comparison to conventional therapy has been investigated in several studies in adults and children.

PTH (1-34)

A series of studies by Winer and colleagues(21) demonstrated that synthetic human PTH (1-34) (hPTH) given once or twice daily, maintained eucalcemia, reduced urine calcium excretion, and increased phosphorus excretion. The effects of PTH (1-34) injections on mineral metabolism differed according to the etiology of HypoPT. Winer and colleagues(22,23) reported in an openlabel, randomized, crossover trial that twice-daily, compared to once-daily PTH (1-34) injections, maintained serum calcium in the near-normal range over 24 hours and significantly reduced the total daily PTH dose from that required under the once-daily regimen. Synthetic hPTH (1-34) was also safe and effective over a 3-year period in both adults and children.(24,25) Furthermore, children treated with hPTH (1-34) in a 3-year randomized parallel trial maintained normal linear growth, weight gain, and renal function with no difference in lumbar spine and whole-body bone mineral density (BMD) Z-scores compared to children receiving conventional therapy. PTH was associated with elevated bone turnover markers compared to conventional therapy.(24,25) Over 10 years, Winer and colleagues(26) reported that children with autoimmune polyendocrine syndrome type 1 (APS-1) or ADH1 treated with PTH (1-34) injections had normal height velocity and bone mineral accretion velocities. The baseline evaluation of nonsurgical HypoPT patients receiving calcitriol and calcium revealed a high prevalence of renal insufficiency or renal calcification.(25–27) There was no change in creatinine clearance for the study duration in the long-term studies of the effects of treatment with hPTH.(25,26) Synthetic hPTH (1-34) has been associated, in one study, with hypocitraturia, a risk factor for renal calcification.(28)

A more physiologic approach, by Winer and colleagues,(29,30) involves continuous delivery of hPTH (1-34) by subcutaneous infusion pump. In a randomized cross-over study comparing hPTH (1-34) delivered by an infusion pump vs twice-daily injections, patients receiving continuous pump delivery manifested normalization of serum calcium with less fluctuation in serum calcium, phosphorus, and magnesium and reduced urine calcium with normalization of bone turnover markers. Daily dose of hPTH (1-34) and magnesium requirements were also significantly reduced with infusion pump delivery of hPTH in comparison to twice daily hPTH (1-34) injections.

Although synthetic hPTH (1-34) is not clinically available, these findings have been replicated with the clinically available recombinant human PTH (1-34) (rhPTH) in adults,(31) children,(32–36) and in infants with refractory, life-threatening HypoPT.(37–39)

PTH (1-84)

Full-length rhPTH (1-84) has been evaluated in placebo controlled and open-label studies.(40–43) The REPLACE study was a 24-week, double-blind, placebo-controlled, phase 3 study conducted in 134 patients randomized to rhPTH (1-84) or placebo. The primary end point (≥50% reduction in calcium and calcitriol doses with maintenance of normal serum calcium) was met in 53% of patients receiving rhPTH (1-84) versus 2% of patients receiving placebo.(41) The decreased need for calcium and active vitamin D supplementation was also observed in both the dose-adjusted(40) (Columbia University) and fixed dose (100 µg/day, Aarhus University)(42) studies. In the randomized controlled trials (RCTs) of rhPTH (1-84), there was no statistically significant difference in urinary calcium excretion between rhPTH and conventional therapy(41,42); however, in the open- label extension of REPLACE, mean urinary calcium level declined into the normal range,(43) similar to what was seen in an 8-year open-label study.(40) Serum phosphorus and the calcium/ phosphorus product decreased in the REPLACE and extension study,(5,6,41,43) findings not replicated in the fixed-dose or adjusted-dose studies.(40,42)

Renal function was found to be stable in the rhPTH (1-84) studies.(40–43) Despite normalization of urine calcium, renal calcifications were not eliminated as nephrolithiasis was still reported in the REPLACE extension study(43) and in the Columbia University study,(40) possibly due to hypocitraturia, but this was not assessed. Hypercalcemia, at various times during the studies, has been observed: 18% in the REPLACE study,(41) 34% in the fixed-dose study,(7,42) and 30% in the Columbia University studies.(40,44) Hypocalcemia was also observed in the RCTs: 38% in the study drug arm versus 23% in placebo in the REPLACE study,(41) 29% in the PTH arm and 53% in the placebo arm in the Aarhus University study,(42) and 13%, with one hospitalization, in the Columbia University study.(8,40)

Effects on bone turnover markers, bone density, and dynamic and structural changes at the tissue level with rhPTH (1-84) are similar to the effects seen with PTH (1-34).(29,30,32) In general, there is an initial marked increase in bone turnover markers, which subsequently decreases and plateaus with long-term treatment. The new steady state is higher than baseline but within the normal reference range. Bone density is in general stable but with decreases observed at the 1/3 radial site. By dynamic histomorphometry as evaluated by bone biopsy, and by high resolution peripheral quantitative computed

tomography (HRpQCT)(9,45) an increase in cortical porosity has been observed.(42–44) The clinical implications of increased cortical porosity are not known, and fracture data are not available.

In the United States, rhPTH (1-84) was approved in 2015 as a once daily subcutaneous administration as an adjunctive treatment for adults with HypoPT not well controlled on conventional therapy.(46) Notably, after discussions with the US Food and Drug Administration, rhPTH was recalled in the United States in September 2019. This was reported to be due to an issue related to rubber particulates originating from the rubber septum of the cartridge.(47) In Europe, rhPTH (1-84) has not been recalled and is approved as add-on therapy to treatment with calcium and active vitamin D supplements when these treatments have been inadequate in the care of HypoPT.

PTH Therapy in Comparison to Conventional Therapy

A systematic review and meta-analysis of the literature from inception to May 2022 was conducted to evaluate the benefits and harms of PTH therapy in comparison to conventional therapy in managing patients with chronic HypoPT.(6) Seven studies met the eligibility criteria listed in Table 2 [siehe Original-LL]. The studies were small, however, and did not report on the eight complications identified as being associated with HypoPT. The studies demonstrate that PTH therapy may enable a larger number of patients to reduce the dose of calcium and active vitamin D by 50% or more. Reductions in serum phosphorus and increases in episodes of hypercalcemia were found to be statistically significant effects of PTH therapy in comparison to conventional therapy. PTH therapy was associated with an increase in bone remodeling reflected by an increase in the biomarkers alkaline phosphatase, osteocalcin, and urine pyridinoline. Serious adverse effects were very infrequent. In the meta-analysis PTH therapy was associated with small improvements in QoL and reduction in pill burden.(6) Because the studies had a very small sample size it was not possible to appreciate the benefits and risks of PTH therapy on patient important outcomes Tables 2 and 3 [siehe Original-LL].

Although studies with PTH (1-34) did not report improvements in QoL(23,29,48) drug efficacy is likely to be affected by the dose and mode of administration as well as the half life of the PTH molecule. Studies with PTH (1-84) therapy demonstrated significant improvements in QoL(49) and this was also observed with the TransCon PTH molecule which has a 60-hour half-life and is currently in phase 3 trials.(50)

Patient Perspective

Members of The HypoPARAthyroidism Association, Inc. believe that a single treatment strategy may not be ideal for all patients. Each patient with HypoPT has different symptoms and complications. Patients think of each person like a snowflake; no two are alike. Many patients feel that conventional therapy keeps them alive, but with poor QoL and at the cost of long-term consequences, including advanced renal disease. Patients often report that their doctors do not understand how to diagnose and treat HypoPT, and frequently minimize or dismiss their symptoms. Great hope was raised when PTH (1-84) was approved, and while it was not ideal for all patients it was progress. Treatment options that will address the underlying cause of HypoPT and improve QoL are needed. The HypoPARAthyroidism Association fully supports the plan of the task force to improve treatment and quality and continuity of care for patients with HypoPT globally.

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Standards of care for hypoparathyroidism in adults: a Canadian and International Consensus

Zielsetzung

To provide practice recommendations for the diagnosis and management of hypoparathyroidism in adults.

Methodik

Methodikeranmerkung: Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund fehlender höherwertiger Evidenz wird die LL ergänzend dargestellt.

Grundlage der Leitlinie

- Repräsentatives Gremium – teilweise dargelegt: Arbeitsgruppe bestehend aus Expertinnen und Experten zur Nebenschilddrüse sowie Allgemeinen Endokrinologinnen und Endokrinologen; Einbindung von Patienteninnen und Patienten nicht identifiziert;
- Interessenkonflikte dargelegt, finanzielle Unabhängigkeit scheint dargelegt: "Funding was received from Canadian Endocrine Update [Organisation nicht identifiziert], McMaster University and Western University for the completion of the literature review – 2018.";
- Systematische Suche, Auswahl und Bewertung der Evidenz dargelegt;
- Formale Konsensusprozesse und externes Begutachtungsverfahren nicht dargelegt: Es bestehen relevante Unsicherheiten, insbesondere zum Entstehungsprozess von Empfehlungen. Es wurde einzig folgende Information identifiziert: The key questions, results of the literature review and practice recommendations were presented at the Endocrine Society annual meeting in March 2018 in a symposium session entitled '2018 Parathyroid Summit: A Focus on Hypoparathyroidism.' The session included time for attendee feedback, which was incorporated into the current manuscript.";
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt - trifft nur teilweise zu: Empfehlungen der Leitlinie wurden nicht bewertet;
- Regelmäßige Überprüfung der Aktualität nicht identifiziert.

Recherche/Suchzeitraum:

We searched PubMed, MEDLINE, EMBASE and Cochrane databases from January 2000 to March 2018 using keywords 'hypoparathyroidism, diagnosis, treatment, calcium, PTH, calcidiol, calcitriol, hydrochlorothiazide and pregnancy'.

LoE

Table 2 Quality assessment criteria (1).

Study design	Quality of evidence	Lower if	Higher if
Randomized trial	High	Risk of bias (–1) Serious (–2) Very serious	Large effect (+1) Large (+2) Very large
	Moderate	Inconsistency (–1) Serious (–2) Very serious	Dose response (+1) Evidence of a gradient
Observational study	Low	Indirectness (–1) Serious (–2) Very serious	All plausible confounding (+1) Would reduce a demonstrated effect or
	Very low	Imprecision (–1) Serious (–2) Very serious Publication bias (–1) Likely (–2) Very likely	(+1) Would suggest a spurious effect when results show no effect

GoR

Nicht vorliegend.

Empfehlungen

2. Management of hypoparathyroidism – avoiding complications of treatment

(a) Are long-term complications a real problem?

Long-term complications include renal impairment, renal stones, nephrocalcinosis as well as cataracts and calcification of the basal ganglia and other regions of the brain (5). Several retrospective studies have shown that long-term complications of hypoparathyroidism are commonly seen. A large cohort study determined the rate of complications in 120 patients with permanent hypoparathyroidism with a mean follow-up of 7.4 years (75). While serum calcium levels were maintained within a calcium range of 7.5–9.5 mg/dL (1.9–2.4 mmol/L) for an average of 86% of the time, the 24-h urinary calcium analysis in 53 patients showed that 38% had a least one measurement with hypercalciuria (>300 mg/day). Renal imaging in 54 patients showed renal calcification was present in 31% of the patient population. Compared with age-appropriate historical controls from NHANES, the rates of chronic kidney disease stage 3 or higher were 2- to 17-fold greater in those with hypoparathyroidism. These data have been recently confirmed in another series of 90 patients with chronic post-surgical hypoparathyroidism (6).

In a large case–control study from a national registry in Denmark, the hazard ratio (HR) for developing kidney stones and renal insufficiency in patients with postsurgical hypoparathyroidism was 4.8 and 3.1, respectively (78). In another Danish case–control study, the HR in patients with nonsurgical hypoparathyroidism for developing renal insufficiency was 6.0 (79).

Cataracts have been reported in approximately 50% of patients with chronic hypoparathyroidism in case series (80, 81). In the case–control studies from Denmark, the risk of cataracts was increased in patients with nonsurgical hypoparathyroidism (HR 4.32) (79), but not in patients with post-surgical hypoparathyroidism (78).

Intracranial calcifications, in particular in the basal ganglia, can develop in patients with hypoparathyroidism (75, 82). The exact cause is not known, however, elevated serum phosphate levels or an elevated calcium-phosphate product are thought to be a contributing factor. The clinical significance of basal ganglia calcifications is unclear; symptoms of Parkinsonism and dystonia have also been described in some cases (82).

Serum phosphate and the calcium-phosphate product should be maintained in the normal reference range (i.e. less than 55 mg2/dL2 (4.4 mmol2 L2)) as they are thought to contribute to extraskeletal calcifications and other complications when elevated (73, 83, 84). This does however require further prospective evaluation. If serum phosphate levels are high, calcium supplements can be increased and should be given with meals as they are excellent phosphate binders. The calcium-phosphate product may not correlate with basal ganglia calcification and this requires further prospective evaluation as well as other measures including serum phosphate and the 24-h urine calcium, which may be of value in predicting the presence of extraskeletal calcification (85). The dose of the active vitamin D can also be reassessed as 1,25(OH)2 increases intestinal calcium absorption as well as phosphorus absorption. Dietary modification with a low phosphate diet (low intake of meat, eggs, cola and dairy) may be implemented as needed on an individual basis. A low-salt diet is also helpful as it lowers renal calcium losses.

Key points:

In hypoparathyroidism, long-term renal complications and extraskeletal calcification are commonly seen and may be reduced by lowering urine calcium excretion, serum phosphorus and the calcium-phosphate product.

Quality of evidence: very low.

(b) How should acute hypocalcemia be managed?

Depending on the rate of onset, biochemical severity and clinical symptoms, acute hypocalcemia may require management in hospital with intravenous calcium. Calcium gluconate is the preferred salt to be administered intravenously as it is less irritating to the veins than calcium chloride. A bolus of 1–2 g of 10% calcium gluconate (corresponding to 90–180 mg of elemental calcium) in 50 mL of 5% dextrose may be administered over 20 min followed by a continuous infusion of intravenous calcium with 1–3 mg/kg/h of elemental calcium administered as calcium gluconate. During the calcium bolus and infusion continuous cardiac monitoring is advised. Oral calcium supplements and active vitamin D are also initiated (83, 86). Hypomagnesemia should be corrected (83) and vitamin D levels should be normalized (2, 3). Low serum magnesium leads to further suppression of PTH synthesis and secretion (87). This paradoxical inhibition of the parathyroid involves intracellular signaling pathways of the CaSR with an increase in the activity of

inhibitory G alpha subunits (57). Hypomagnesemia also results in a resistance to the effects of PTH in the tissues. PTH induced bone resorption is impaired in hypomagnesemia (88, 89, 90). Intracellular Mg2+ is a cofactor of adenylate cyclase and decreases in intracellular ionized Mg2+ lead to resistance to PTH (91, 92, 93). Hypocalcemia combined with magnesium deficiency is resistant to treatment with Ca2+ or vitamin D, but rapidly responds to Mg2+ supplementation.

There are very little data (largely from case reports) regarding the possible use of rhPTH (1–84) in the management of acute hypocalcemia (94, 95, 96). Hypoparathyroidism is associated with impaired hydroxylation of 25 hydroxyvitamin D in the kidney as PTH stimulates the formation of 1,25 dihydroxyvitamin D (calcitriol) (97). Therefore, individuals with hypoparathyroidism have a deficiency of both PTH as well as calcitriol. Active vitamin D metabolites are necessary to correct the hypocalcemia and enhance the intestinal absorption of both calcium and phosphate. Calcitriol can be initiated with doses of 0.25 µg twice daily and gradually titrated upward to a dose of 2.0 µg BID if necessary (2). Occasionally higher doses may be necessary. The halflife of calcitriol is 5–8 h and the dose can be increased in 48–72 h. Alfacalcidiol (1alpha (OH) D3) can also be used in doses of 0.5–4 µg once daily; however, it has a longer time to offset of action (5–7 days) and is not as potent as calcitriol (98, 99). Close titration is required to avoid hypercalciuria and hypercalcemia which may contribute to the long-term complications of renal and extra skeletal calcification. Parent vitamin D (D2 or ergocalciferol or D3 cholecalciferol) is of value to ensure that the 25hydroxyvitamin D levels are in the normal reference range (75 nmol/L or higher) (100).

Key recommendation:

Acute severe hypocalcemia is treated with IV calcium boluses followed by a continuous calcium infusion as well as oral calcium supplements and active vitamin D. Hypomagnesemia must be corrected.

Quality of evidence: low (standard practice).

(c) What are practical strategies to lower urinary calcium?

Reducing the filtered renal load of calcium by decreasing serum calcium is the most effective method to lower urinary calcium in chronic hypoparathyroidism. Thiazide diuretics may also be effective in lowering urinary calcium losses especially when combined with a low-salt diet (101). For individuals with ADH type 1 (ADH 1) and ADH 2, thiazide diuretics may further exacerbate the hypokalemia; therefore, extreme caution must be exercised. Distributing calcium supplements evenly throughout the day can avoid peaks of serum calcium, which may contribute to hypercalciuria. Finally, rhPTH(1–84) replacement therapy may also be considered as discussed below (74).

Key recommendation:

Reduce urinary calcium losses with a low-salt diet and consider hydrocholorothiazide, chlorthalidone or indapamide as tolerated. In the presence of renal complications rhPTH(1–84) may also be considered.

Quality of evidence: low.

Methodikeranmerkung: Empfehlungen und Hintergrundinformationen zu Kapitel „3. Management of hypoparathyroidism in pregnancy and lactation“ können der Original-LL entnommen werden.

4. rhPTH(1–84) replacement therapy in hypoparathyroidism – when and how to proceed?

A number of key questions arise when considering which patients with chronic hypoparathyroidism should be treated with rhPTH(1–84) replacement therapy. Replacement therapy with rhPTH(1–84) has been approved as an adjunct to conventional therapy by regulatory agencies.

(a) Which criteria confirm that conventional therapy for chronic hypoparathyroidism has failed?

Limitations of conventional therapy with calcium, active vitamin D metabolites and vitamin D include an inability to alleviate the symptoms of hypocalcemia and to improve quality of life. In the absence of PTH, urinary calcium excretion is elevated and contributes to the long-term complications of hypoparathyroidism which include renal insufficiency, nephrocalcinosis as well as nephrolithiasis (153). Guidelines define failure of conventional treatment of chronic hypoparathyroidism as meeting certain

criteria (73, 74): (1) inability to keep serum calcium in the lower half of reference range without symptoms of hypocalcemia, (2) failure to keep serum phosphate within the reference range, (3) inability to keep the calcium-phosphorus product below 55 mg2/ dL2 (4.4 mmol2 L2), (4) failure to keep serum magnesium within the reference range, (5) inability to keep urinary calcium within the reference range for weight and gender and 6) failure to maintain long-term well-being and QOL.

In addition, compliance with conventional therapy is often poor and is contributed to by the large number of pills required daily as well as gastrointestinal side effects of supplemental calcium.

Key recommendation:

Failure of conventional therapy is confirmed in the presence of poor control of serum calcium, the presence of complications of hypoparathyroidism or the presence of a poor quality of life.

Quality of evidence: low-moderate.

(b) When should rhPTH(1–84) replacement therapy be considered in patients with chronic hypoparathyroidism?

PTH replacement therapy was initially evaluated in hypoparathyroidism with the PTH(1–34) molecule. Subcutaneous twice daily injections of PTH(1–34) maintained mean urine calcium in the normal range, with no difference compared to calcitriol (154, 155), whereas intravenous administration using a pump resulted in a marked decline in mean urine calcium well within the normal range, with a significant difference in comparison to calcitriol (156). More recently, PTH(1–34) in doses of 20 µg BID led to reductions in the dose of calcium and calcitriol required daily and increased serum calcium while lowering serum phosphate (157, 158) […].

Replacement therapy with PTH(1–84) maintains serum calcium and phosphate levels in the appropriate range, while reducing the daily doses of calcium and active vitamin D metabolites (159, 160). In some patients PTH replacement therapy enables withdrawal of calcium and active vitamin D analogs. The effects on urinary calcium excretion are modest; however, a long-term open-label study suggests a progressive decrease in urinary calcium excretion (161) […]. Skeletal abnormalities (low turnover status, increased bone mineral density (BMD)) are improved. Bone turnover markers increase within 1 year and subsequently decline to levels that are higher than pretreatment values. BMD increases at the lumbar spine and to a lesser extent at the hip, while there is a progressive decline at the distal 1/3 radius (161). Bone histomorphometry studies have shown reductions in trabecular width and an increase in trabecular number. Intratrabecular tunneling has been demonstrated in about half of the biopsy specimens (161). Cancellous bone matrix mineralization is markedly increased in hypoparathyroid bone compared to normal. rhPTH(1–84) treatment after 1 year is associated with a decrease in the degree of mineralization which returns to the baseline value at year 2 (162). Conversely, the greater heterogeneity detected at 1 year persists (162).

Recently, an increased rate of vertebral fractures has been reported in patients with idiopathic hypoparathyroidism treated with conventional therapy (81). Replacement therapy with rhPTH(1–84) may have positive skeletal effects on bone strength and fracture risk; however, this requires further evaluation […].

Several studies have shown that quality of life is reduced in patients with hypoparathyroidism (163, 164, 165, 166). Short-term placebo-controlled studies have shown either no effect or modest improvement, whereas a long-term open-label study has shown a benefit in all parameters of the SF-36 scale (163).

PTH replacement therapy is well tolerated and adverse events are mild and transient.

No data are currently available on the potential long-term benefits of rhPTH(1–84) replacement therapy. The FDA has approved rhPTH(1–84) with a ‘black box’ warning because of an increased risk of osteosarcoma in rats treated with high doses of PTH(1–34); however, an increased rate of osteosarcoma has not been observed in humans despite use in more than a million people (167).

As PTH therapy in hypoparathyroidism has been demonstrated to lower the requirements for calcium and active vitamin D analogs and also lower serum phosphate as well in some studies demonstrated reductions urinary calcium excretion, it has been proposed that PTH replacement be considered in the following circumstances;

1. inadequate control of serum calcium,
2. oral calcium or vitamin D medications required to control serum calcium or symptoms that exceed 2.5 g calcium or >1.5 µg calcitriol per day,

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 mg2 dL2 (4.4 mmol2 L2) (74).

There are many factors contributing to urine calcium including the filtered calcium load as well as the dose of PTH and frequency of administration of this molecule. Further prospective data will enable refinement of administration with a goal to consistently reduce urine calcium excretion.

PTH replacement may also be of value in individuals who have malabsorption or are intolerant of large doses of oral calcium supplements as well as those who are noncompliant with taking several pills each day. PTH replacement therapy may improve quality of life; however, effects of PTH replacement on quality of life require further study as currently controlled studies have not demonstrated reversal of muscle weakness and fatigue with therapy. Wide fluctuations in serum calcium may occur in certain individuals with hypoparathyroidism particularly following exercise or with intercurrent illness and may result in hospitalization. Overcorrection of hypocalcemia may lead to hypercalcemia and individuals with wide fluctuations in serum calcium require close monitoring ideally with a calcimeter which can provide immediate measures of serum calcium in real time.

Having such devices easily available to patients will enable assessment of serum calcium with the onset of symptoms and allow closer titration of therapy based on current serum calcium. Such close monitoring is expected to revolutionize care for hypoparathyroidism similar to the enhanced care possible for diabetes with the advent of glucometers. Calcimeters have been developed and are expected to be released for general use in the near future. The approved indications for PTH replacement therapy may vary depending on the regulatory authorities of each country.

Key recommendation:

rhPTH(1–84) replacement therapy may be considered if the serum calcium is poorly controlled, high doses of calcium or active vitamin D are required, renal complications are present or quality of life is poor or gastrointestinal malabsorption is present.

Quality of evidence: low.

(c) Once rhPTH(1–84) replacement therapy is started, how should therapy be titrated?

The FDA approved starting rhPTH(1–84) at a dose of 50 µg by subcutaneous injection once each day with a concomitant 50% decrease in the dose of active vitamin D metabolites (83, 167). After an appropriate interval of several weeks, the dose may be increased to 75 µg each day, and then 100 µg each day after several more weeks, or reduced to 25 µg each day, as required to meet treatment goals, aiming to discontinue the active vitamin D and reduce calcium supplements to 500 mg daily.

Key recommendation:

rhPTH(1–84) replacement therapy can be initiated at a 50 µg daily dose with close monitoring of serum calcium and phosphate. The dose of rhPTH (1–84) can be gradually titrated upwards or downwards based on the lab profile and the doses of serum calcium and active vitamin D can also be gradually reduced as the dose of the rhPTH(1–84) is gradually increased.

Quality of evidence: low-moderate.

(d) If rhPTH(1–84) replacement therapy is initiated, should it ever be stopped?

This is left to the judgment of the treating physician. rhPTH(1–84) replacement therapy may be stopped if treatment goals cannot be achieved despite appropriate dose adjustment, or patients are unable to tolerate or comply with therapy for any reason. Discontinuation of rhPTH(1–84) requires gradual reductions in the dose over several weeks as abrupt cessation has been associated with hypocalcemia, which may reflect increased bone remodeling favoring formation leading to the hungry bone syndrome (168). While decreasing the rhPTH(1–84) dose treatment with active vitamin D metabolites should be restarted or adjusted, as appropriate.

Key recommendation:

Stop therapy if the treatment goals cannot be achieved despite appropriate dose adjustment or if the patient is unable to tolerate or comply with therapy for any reason. Quality of evidence: low-moderate.

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4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 05 of 12, May 2023) am 08.05.2023

#	Suchfrage
1	[mh hypoparathyroidism]
2	hypoparathyroid*:ti,ab,kw
3	#1 OR #2
4	#3 with Cochrane Library publication date from May 2018 to May 2023

Systematic Reviews in PubMed am 08.05.2023

verwendete Suchfilter:
Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 14.02.2023.

#	Suchfrage
1	hypoparathyroidism[mh]
2	hypoparathyroid*[tiab]
3	#1 OR #2
4	(#3) AND (systematic review[ptyp] OR meta-analysis[ptyp] OR network meta-analysis[mh] OR (systematic*[tiab] AND (review*[tiab] OR overview*[tiab])) OR metareview*[tiab] OR umbrella review*[tiab] OR "overview of reviews"[tiab] OR meta-analy*[tiab] OR metaanaly*[tiab] OR metanaly*[tiab] OR meta-synthes*[tiab] OR metasynthes*[tiab] OR meta-study[tiab] OR metastudy[tiab] OR integrative review[tiab] OR integrative literature review[tiab] OR evidence review[tiab] OR ((evidence-based medicine[mh] OR evidence synthes*[tiab]) AND review[pt]) OR ((("evidence based" [tiab:~3]) OR evidence base[tiab]) AND (review*[tiab] OR overview*[tiab])) OR (review[ti] AND (comprehensive[ti] OR studies[ti] OR trials[ti])) OR ((critical appraisal*[tiab] OR critically appraise*[tiab] OR study selection[tiab] OR ((predetermined[tiab] OR inclusion[tiab] OR selection[tiab] OR eligibility[tiab]) AND criteri*[tiab]) OR exclusion criteri*[tiab] OR screening criteri*[tiab] OR systematic*[tiab] OR data extraction*[tiab] OR data synthes*[tiab] OR prisma*[tiab] OR moose[tiab] OR entreq[tiab] OR mecir[tiab] OR stard[tiab] OR strobe[tiab] OR "risk of bias"[tiab]) AND (survey*[tiab] OR overview*[tiab] OR review*[tiab] OR search*[tiab] OR analysis[ti] OR apprais*[tiab] OR research*[tiab] OR synthes*[tiab]) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR bibliographies[tiab] OR published[tiab] OR citations[tiab] OR database*[tiab] OR references[tiab] OR reference-list*[tiab] OR papers[tiab] OR trials[tiab] OR studies[tiab] OR medline[tiab] OR embase[tiab] OR cochrane[tiab] OR pubmed[tiab] OR "web of science" [tiab] OR cinahl[tiab] OR cinhal[tiab] OR scisearch[tiab] OR ovid[tiab] OR ebsco[tiab] OR scopus[tiab] OR epistemonikos[tiab] OR prospero[tiab] OR proquest[tiab] OR lilacs[tiab] OR biosis[tiab])) OR technical report[ptyp] OR HTA[tiab] OR technology assessment*[tiab] OR technology report*[tiab])

#	Suchfrage
5	((#4) AND ("2018/05/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))
6	(#5) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])

Leitlinien in PubMed am 08.05.2023

verwendete Suchfilter:
Konsentierter Standardfilter für Leitlinien (LL), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 21.06.2017.

#	Suchfrage
1	hypoparathyroidism[mh]
2	hypoparathyroid*[tiab]
3	#1 OR #2
4	(#3) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] *OR recommendation*[ti])*
5	(((#4) AND ("2018/02/01"[PDAT] : "3000"[PDAT])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp])) NOT ("The Cochrane database of systematic reviews"[Journal]) NOT ((comment[ptyp]) OR letter[ptyp]))
6	(#5) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])

Iterative Handsuche nach grauer Literatur, abgeschlossen am 08.05.2023

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- Nationale VersorgungsLeitlinien (NVL)

- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)

- ECRI Guidelines Trust (ECRI)
- Dynamed / EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

Referenzen

1. **Edafe O, Mech C, Balasubramanian S.** Calcium, vitamin D or recombinant parathyroid hormone for managing post-thyroidectomy hypoparathyroidism. Cochrane Database of Systematic Reviews [online]. 2019(5). URL: http://dx.doi.org/10.1002/14651858.CD012845.pub2.
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[A] **Rethlefsen ML, Kirtley S, Waffenschmidt S, Ayala AP, Moher D, Page MJ, et al.** PRISMA-S: an extension to the PRISMA Statement for Reporting Literature Searches in Systematic Reviews. Syst Rev 2021;10(1):39. https://doi.org/10.1186/s13643-020-01542-z

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Beteiligung von Fachgesellschaften und der AkdÄ zu Fragen der Vergleichstherapie nach §35a Abs. 7 SGB V i.V.m. VerfO 5. Kapitel § 7 Abs. 6

Verfahrens-Nr.: 2023-B-110

Verfasser	
Name der Institution	Deutsche Gesellschaft für Endokrinologie (DGE)
Datum der Erstellung	20. Juni 2023

(Bei mehreren beteiligten Fachgesellschaften bitte mit entsprechenden Angaben.)

Indikation
PTH-Ersatztherapie für die Behandlung von Hypoparathyreoidismus bei Erwachsenen.
Fragen zur Vergleichstherapie
Was ist der Behandlungsstandard in o.g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus? *(Bitte begründen Sie Ihre Ausführungen; geben Sie ggf. zitierte Quellen in einer Referenzliste an.)*

Einleitung

Als Hypoparathyreoidismus wird eine Erkrankung bezeichnet, die mit einer verminderten Sekretion von Parathormon (PTH) einhergeht und durch eine Hypokalzämie, Hyperphosphatämie und Hyperkalzurie charakterisiert ist (1). Zu den Ursachen zählen eine Schädigung der Nebenschilddrüsen, eine genetische Erkrankung der Epithelkörperchen oder eine akute reversible Funktionsstörung (z.B. bei Magnesiummangel)(2). Am häufigsten ist der PTH-Mangel durch eine versehentliche Entfernung oder Verletzung der Nebenschilddrüsen während einer Operation im Halsbereich bedingt, z. B. im Rahmen einer totalen Thyreoidektomie oder einer Neck-Dissection bei Kopf-Hals-Tumoren (postoperativer Hypoparathyreoidismus).

Der Hypoparathyreoidismus ist selten, die Prävalenzzahlen schwanken je nach untersuchter Population. Nach einer Hochrechnung aus Versicherungsdaten wird die Gesamtprävalenz in den USA auf 37/100.000 Personenjahre geschätzt (3), die des postoperativen Hypoparathyreoidismus auf 19/100.000 (3). Populationsbasierte Studien aus Dänemark und Schottland zeigen eine vergleichbare Prävalenz des postoperativen Hypoparathyreoidismus von 22/100.000 (4, 5).

Der nicht-chirurgische Hypoparathyreoidismus ist deutlich seltener als der postoperative; je nach untersuchter Population beträgt dessen Prävalenz zwischen 0,7 und 5/100.000 (4).

In Deutschland existieren keine belastbaren Prävalenzdaten. Hochgerechnet aus der Anzahl der Schilddrüsenoperationen und dem Risiko eines permanenten Hypoparathyreoidismus von 1–2 % wäre eine Prävalenz von 1–2/100.000 zu erwarten. Tatsächlich liegt sie jedoch u. a. wegen der nicht vollständigen Erfassung von Operationen im Halsbereich, eines höheren Risikos für Hypoparathyreoidismus bei chirurgischen Eingriffen außerhalb von spezialisierten Zentren und Schwierigkeiten bei der Diagnosestellung mit hoher Wahrscheinlichkeit höher.
Ein bisher wenig beachtetes und schwierig zu operierendes Kollektiv stellen Kinder dar, von denen 7,3 % nach totaler Thyreoidektomie einen permanenten Hypoparathyreoidismus entwickeln (6).

Zur Therapie des Hypoparathyreodismus stehen aktuell drei Publikationen zur Verfügung. Neben der Leitlinie der Europäischen Gesellschaft für Endokrinologie aus dem Jahr 2015 (7) wurden 2022 europäische Empfehlungen publiziert (8) und ebenfalls 2022 eine internationale Leitlinie zum Hypoparathyreoidismus (9). Allen diesen Publikationen zufolge besteht der Therapiestandard derzeit aus der Gabe von aktiviertem Vitamin D und Kalzium in aufgeteilten Dosierungen in Kombination mit genuinem Vitamin D und Magnesium (schwache Empfehlung, niedrige Evidenz). Wenn diese Therapie nicht ausreichend oder nicht zufriedenstellend ist, kann eine Therapie mit Parathormon in Erwägung gezogen werden (9).

Konventionelle Therapie

Aktuell sind in Deutschland als aktive Vitamin D Präparate Calcitriol und Alfacalcidol für die Therapie erhätlich. Das früher viel verwendetet Dihydrotachysterol ist nicht mehr verfügbar. Nach der Literatur haben beide Präparate vergleichbare Effekte und führen bei optimaler Calciumeinstellung zu vergleichbar hohen Phosphatwerten und zu einer erhöhten Calciumausscheidung (10).

Präparat	Relative Potenz	Wirkeintritt / Wirkdauer	Ungefähre Tagesdosis
Alfacalcidol (1-alpha-Hydroxy- Vitamin D3)	Ca. 1000	1-2 Tage 5-7 Tage	1-3 µg
Calcitriol (1,25-Dihydroxy- Vitamin-D3)	1.000-1.500	1-2 Tage	0,5-2 µg

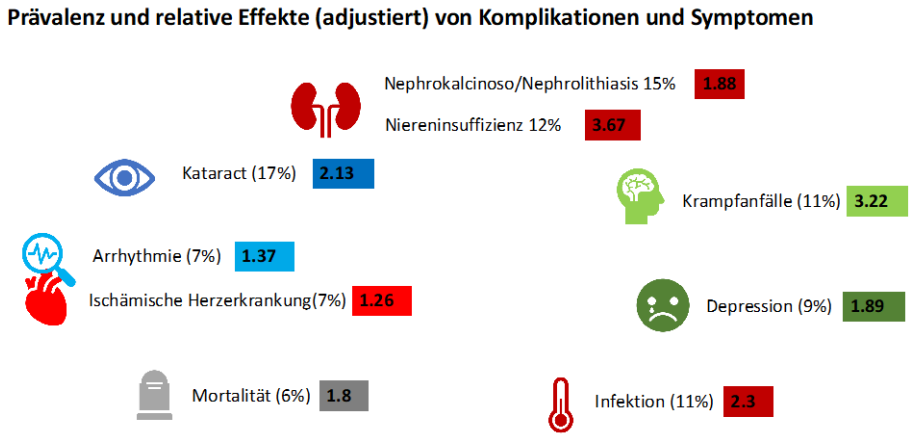
		2-3 Tage	

Die Therapie mit aktivem Vitamin D ersetzt die Funktionen von PTH nicht vollständig und ist mit langfristigen Komplikationen assoziiert. Das aktive Vitamin D kann das Calcium im Blut anheben durch vermehrte Resorption im Darm, kann aber den Calciumverlust über die Niere nicht steuern und führt auch zu einer vermehrten Resorption von Phosphat, was zu einem erhöhten Calcium-Phosphat-Produkt führt. Parathormon regelt die Calcium- und Phosphatausscheidung über die Niere, was von aktivem Vitamin D nicht übernommen werden kann.

Komplikationen und Symptome

Die Komplikationen des Hypoparathyreoidismus wurden in einer kürzlichen systematischen Metaanalyse herausgearbeitet (11). Für jeden angegebenen Komplikation mussten mindestens zwei Studien vorliegen, und jeweils im Vergleich zu Kontrollen ohne Hypoparathyreoidismus. In der Abbildung 2 sind die Komplikationen und der relative Effekt dargestellt.

Abb. 2:



Yao. L. et al. . (2022). Complications. Symptoms. Pre-surgical Predictors in Patients with Chronic Hypoparathyroidism: A Systematic Review. J Bone Miner Res. Accepted Author Manuscript.https://doi.org/10.1002/jbmr.4673

Symptome und Komplikationen sind somit vielfältig unter der aktuell durchgeführten sogenannten konventionellen Therapie. Als Ursachen der Komplikationen und Symptome werden vor allem hyperkalzämische Phasen, hohe Phosphatwerte und ein erhöhtes Calcium-Phosphat Produkt verantwortlich gemacht (12). Auch die Lebensqualität gemessen mit

spezifischen Fragebögen korreliert zu den biochemischen Parametern und der Therapie (13, 14).

Assoziation zwischen Risiko von Langzeitkomplikationen und abweichender Laborparameter anhand einer dänischen Studie bei 431 Patienten mit HPT:

Biochemische Parameter		Risiko für Langzeitkomplikation*
Niedrige Ca^{2+} Werte, mmol/L	≤1,15	• Erhöhtes Kardiovaskuläres Risiko (OR 3,01; 95% KI 1,03–0,82)
Hohe P Werte, $mmol^2/L^2$	≥1,28	• Erhöhtes Mortalitätsrisiko (OR 8,43; 95% KI 2,26–31,53) • Erhöhtes Risiko für Infektionen (OR 2,18; 95% KI 1,12–4,26)
Hohe Ca x P Produkt Werte, $mmol^2/L^2$	≥2,62	• Erhöhtes Mortalitätsrisiko† (OR 4,47; 95% KI 1,11–17,94)
	≥2,93	• Erhöhtes Risiko für renale Komplikationen (OR 2,07; 95% KI 1,04–4,14)
Anzahl der hypercalcämischen Krisen, n	1 to 3	• Erhöhtes Mortalitätsrisiko (OR 3,39; 95% KI 1,05–10,91) • Erhöhtes Risiko für renale Komplikationen (OR 3,05; 95% KI 1,56–5,97)
	≥4	• Erhöhtes Kardiovaskuläres Risiko (OR 9,69; 95% KI 2,63–35,79) • Erhöhtes Risiko für renale Komplikationen (OR 3,31; 95% KI 1,55–7,08) • Erhöhtes Risiko für Infektionen (OR 2,74; 95% KI 1,19–5,14)

*Alle $P<0,05$; †Hinweis: für $CaxP_{tw}$ ≥2.93 $mmol^2/L^2$ lag das erhöhte Risiko für Mortalität bei OR 6,85; 95% KI 1,75–28,88.
Ca, Kalzium; CaxP, Kalzium-Phosphate Product; KI, Konfidenzintervall; CVD, kardiovaskuläre Erkrankung; OR, adjustierte Odds Ratio; P, Phosphat; tw, zeit-gewichtete durchschnittliche Konzentrationen; HPT, Hypoparathyreoidismus.

Underbjerg L, et al. J Bone Miner Res. 2018;33(5):822-831

Hormontherapie

Der Hypoparathyreoidismus ist die einzige endokrine Erkrankung, bei der bisher nicht das fehlende Hormon ersetzt wird, sondern eine Ersatzmedikation erfolgt. Nach den aktuellen Leitlinien wird die Hormontherapie empfohlen, wenn die konventionelle Therapie nicht zufriedenstellend durchgeführt werden kann. Ziel der Therapie sind in der folgenden Tabelle dargestellt (7) und entsprechen auch den Zielen der internationalen Leitlinien:

Therapieziele
Empfehlungen und Vorschläge gemäß ESE

Therapieziele gemäß Leitlinien der European Society of Endocrinology (ESE, 2015)[1]

Vorschläge:

1. Einstellung des Calcium-Levels im Serum im unteren Normalbereich oder minimal erniedrigt*
2. Calcium-Ausscheidung über 24h soll innerhalb des geschlechtsspezifischen Intervalls liegen*
3. Phosphat-Wert im Serum soll innerhalb des Referenz-Intervalls liegen*
4. Calcium-Phosphat-Produkt im Serum soll < 4,4 $mmol^2/l^2$ (55 mg^2/dl^2) sein*
5. Magnesium-Wert im Serum soll innerhalb des Referenz-Intervalls liegen*
6. Einstellung eines adäquaten Vitamin D Status*

Empfehlungen:

1. Optimierung des persönlichen Wohlbefindens der Patienten
2. Aufklärung der Patienten

* Qualität der zugrunde liegenden Evidenz wird als sehr gering eingeschätzt

[1] Bollerslev J et al. Eur J Endocrinol. 2015 Aug;173(2):G1-20.

Als Beispiele für die Indikation zu einer Hormonersatztherapie werden angegeben: symptomatische Hypokalziämie, Hyperphosphatämie, Niereninsuffizienz, Hyperkalziurie, reduzierte Lebensqualität, schlechte Compliance, Malabsorption /z.B. nach Adipositatsoperation, entzündliche Darmerkrankung), sehr hohe Dosen Calcium (> 2 g tgl) oder aktiven Vitamin D (> 2 µg tgl.) (9). Bei Tagesdosen von 2 g Kalzium oder mehr kommt es häufig zu abdominellen Beschwerden und Diarrhoen.

Versorgungspraxis

In Deutschland liegen keine zuverlässigen Daten zum aktuellen Therapievorgehen vor. Die Standardeinstellung wird nach wie vor mit konventioneller Therapie durchgeführt. Die Therapie mit rekombinantem Parathormon (Natpar®) ist zugelassen nur dann, wenn mit konventioneller Therapie keine adäquate Einstellung erreicht werden kann und bleibt somit nur wenigen Betroffenen vorbehalten. Das Präparat ist allerdings nur bis Ende des Jahres 2024 verfügbar, die Firma Takeda hat im Oktober 2022 mitgeteilt, dass sie das Medikament wegen Produktionsproblemen vom Markt nehmen.

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen in der o.g. Indikation, die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?
(Bitte begründen Sie Ihre Ausführungen; geben Sie ggf. zitierte Quellen in einer Referenzliste an.)

Im Rahmen einer Schilddrüsenoperation und anderen Eingriffen im Halsbereich können durch Manipulation, Devaskularisierung oder akzidentelle Entfernung Schäden an Nebenschilddrüsen entstehen. Bei zwei Drittel der Patienten normalisiert sich die postoperativ zunächst erniedrigte PTH-Sekretion innerhalb von 4–6 Wochen nach der Operation, bei mehr als 90 % innerhalb von 6 Monaten (7). Die Zeit bis zur Erholung des PTH-Werts bei transientem Hypoparathyreoidismus kann jedoch stark variieren und teilweise mehr als 1 Jahr betragen(15). Ein Zeitraum von 12 Monaten ist daher gut geeignet, um einen permanenten Hypoparathyreoidismus nach der Operation zu definieren. Dieser wird auch von den Leitlinien als Zeitpunkt der Definition eines chronischen Hypoparathyreoidismus angegeben (9).

Somit werden Betroffene mit einem postoperativen Hypoparathyreoidismus im ersten Jahr mit einer konventionellen Therapie eingestellt. In dieser Zeit und im weiteren Verlauf wird versucht die Parameter in den Zielbereich einstellen. Zum Monitoring existiert nahezu keine wissenschaftliche Literatur. International wurde daher eine Expertenbefragung durchgeführt um Empfehlungen zu Kontrollintervallen auszusprechen (16). Somit ist die Therapie auf Best-practice Konzepte angewiesen. Kommt es zu einer ausgeprägten Hyperkalziurie können

Thiaziddiuretika verwendet werden, um die Calciumausscheidung zu reduzieren. Für HCT liegt allerdings ein Rote- Hand-Brief vor, so dass dieses Medikament für die Langzeittherapie nicht in Frage kommt. Alternativ können Chlorthalidon oder Indapamid für die Therapie verwendet werden. Bei erhöhten Phosphatspiegeln kann eine Ernährungsberatung empfohlen werden, ist aber nicht so häufig hilfreich. Die Einnahme von Calcium zu den Mahlzeiten bindet Phosphat und kann helfen den Spiegel zu senken. Daten zu Phosphatbindern bei der Indikation liegen nicht vor, werden in seltenen Fällen kursorisch verwendet. Werden die Therapieziele nicht erreicht oder gibt es Hinweise für Organschäden (eingeschränkte Nierenfunktion, Nierensteine, Nephrokalzinose, Basalganglienverkalkung, Katarakt) oder eine deutlich reduzierte Lebensqualität mit multipler Beschwerdesymptomatik durch die Erkrankung oder die durchgeführte Therapie kann ein Therapieversuch mit rekombinantem Parathormon erfolgen. In Deutschland ist dafür aktuell rhPTH 1-84 (Natpar®) zugelassen, in anderen europäischen Ländern wird dafür auch Teriparatid (PTH1-34) verwendet, was in Deutschland aber nur für die Therapie der manifesten postmenopausalen Osteoporose zugelassen ist. Daten zur Langzeittherapie mit rekombinantem Parathormon liegen bei Kindern und Erwachsenen bei der insgesamt seltenen Erkrankung nur bei wenigen Betroffenen vor, immerhin gelingt eine Therapie über 5-8 Jahre ohne weitere Komplikationen mit einer gebesserten Lebensqualität vor allem bei denen, bei denen sie zu Beginn extrem eingeschränkt war (17-20).

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