Abstract

Hypoparathyroidism (HypoPT) is a rare (orphan) endocrine disease with low calcium and inappropriately low (insufficient) circulating PTH levels, most often in adults secondary to thyroid surgery. Standard treatment is activated vitamin D analogues and calcium supplement and not replacement with the lacking hormone, as in other hormonal deficiency states.

The purpose of this guideline is to provide clinicians with guidance on the treatment and monitoring of chronic HypoPT in adults who do not have end-stage renal disease. We intend to draft a practical guideline, focusing on operationalized recommendations deemed to be useful in the daily management of patients.

This guideline was developed and solely sponsored by The European Society of Endocrinology, supported by CBO (Dutch Institute for Health Care Improvement) and based on the GRADE principles as methodological base. The clinical question on which the systematic literature search was based and for which available evidence was synthesized was: What is the best treatment for adult patients with chronic HypoPT? This systematic search found 1,100 articles, reduced to 312 based on title and abstract. The working group assessed these for eligibility in more details, 32 articles were assessed in full-text. Of note, for the final recommendations also other literature was taken into account.

Little evidence is available on how best to treat HypoPT. Data on quality of life and the risk of complications have just started to emerge, and clinical trials on how to optimize therapy is essentially non-existent. Most studies are of limited sample size, hampering firm conclusion. No studies are available relating target calcium levels to clinically relevant endpoints. Hence it is not possible to formulate recommendations based on strict evidence. This guideline is therefore mainly based on how patients are managed in clinical practice, as reported in small case series and based on the experiences of the authors.
1. **Summary of Recommendations**

1.1. **Diagnosis**

1.1.1 We recommend considering a diagnosis of chronic hypoparathyroidism (HypoPT) in a patient with hypocalcaemia and inappropriately low PTH levels.

1.1.2 We suggest considering genetic testing and/or family screening in a patient with HypoPT of unknown etiology.

1.2. **General goals of management in chronic hypoparathyroidism**

1.2.1 We suggest treatment targeted to maintain serum calcium level (albumin adjusted total calcium or ionized calcium) in the lower part or slightly below the lower limit of the reference range (target range) with patients being free of symptoms or signs of hypocalcaemia.

1.2.2 We suggest that 24-hour urinary calcium excretion should be within the sex-specific reference range.

1.2.3 We suggest that serum phosphate levels should be within the reference range.

1.2.4 We suggest that the serum calcium–phosphate product should be below 4.4 mmol$^2$/L$^2$ (55 mg$^2$/dL$^2$).

1.2.5 We suggest that serum magnesium levels should be within the reference range.

1.2.6 We suggest aiming at an adequate vitamin D status.

1.2.7 We recommend that treatment be personalized and focused on the overall well-being and quality of life (QoL) of the patient when implementing different therapeutic efforts, aiming to achieve the therapeutic goals.

1.2.8 We recommend providing information/education that enables patients to know the possible symptoms of hypo- or hypercalcaemia and/or complications of their disease.

1.3. **Treatment**

1.3.1 We recommend treatment of all patients with chronic HypoPT with symptoms of hypocalcaemia and/or an albumin adjusted serum calcium level < 2.0 mmol/L (< 8.0 mg/dL) / ionized serum calcium (S-Ca$^{2+}$) levels < 1.00 mmol/L).

1.3.2 We suggest offering treatment to asymptomatic patients with chronic HypoPT and an albumin adjusted calcium level between 2.0 mmol/L (8.0 mg/dL / S-Ca$^{2+}$ 1.10 mmol/L) and the lower limit of the reference range in order to assess whether this may improve their well-being.

1.3.3 We recommend the use of activated vitamin D analogues plus calcium supplements in divided doses as the primary therapy.
1.3.4 If activated vitamin D analogues are not available, we recommend treatment with calciferol (preferentially cholecalciferol).

1.3.5 We recommend that the doses of activated vitamin D analogues or cholecalciferol are titrated in such a manner that patients are without symptoms of hypocalcaemia and serum calcium levels are maintained within the target range.

1.3.6 We recommend vitamin D supplementations in a daily dose of 1000-2000 IU to patients treated with activated vitamin D analogues.

1.3.7 In a patient with hypercalciuria, we suggest considering a reduction in calcium intake, a sodium-restricted diet, and treatment with a thiazide diuretic.

1.3.8 In a patient with renal stones, we recommend evaluation of renal stone risk factors and management according to relevant international guidelines.

1.3.9 In a patient with hyperphosphataemia and/or an elevated calcium-phosphate product, we suggest considering dietary interventions and/or adjustment of treatment with calcium and vitamin D analogues.

1.3.10 In a patient with hypomagnesaemia, we suggest considering measures that may increase serum magnesium levels.

1.3.11 We recommend against the routine use of replacement therapy with PTH or PTH analogues.

1.4. Monitoring

1.4.1 We recommend routine biochemical monitoring of serum levels ionized or albumin adjusted total calcium, phosphate, magnesium and creatinine (estimated glomerular filtration rate, eGFR), as well as assessment of symptoms of hypocalcaemia and hypercalcaemia at regular time intervals (e.g., every 3-6 months).

1.4.2 Following changes in therapy, we recommend biochemical monitoring weekly or every other week.

1.4.3 We suggest considering monitoring of 24-hour urinary calcium excretion at regular, but longer time intervals (e.g., once a year or every second year).

1.4.4 We recommend renal imaging if a patient has symptoms of renal stone disease or if serum creatinine levels start to rise.

1.4.5 We suggest monitoring for development of signs or symptoms of co-morbidities at regular time intervals (e.g., yearly).

1.4.6 We advise against routine monitoring of bone mineral density by dual energy X-ray absorptiometry (DXA) scans.

1.5. Special circumstances
Autosomal dominant hypocalcaemia (ADH):

1.5.1 We recommend frequent monitoring of patients with ADH, who are being treated with calcium and/or activated vitamin D analogues, as such patients may be at high risk of hypercalciiuria and renal complications.

Pregnancy and breastfeeding:

1.5.2 We suggest treatment with activated vitamin D analogues and calcium supplements as in non-pregnant patients.

1.5.3 We suggest monitoring serum ionized calcium regularly (every 2nd or 3rd week) during pregnancy and breastfeeding with levels to be kept at the lower end of the normal range (serum albumin adjusted total calcium is also acceptable).

2. Methods

2.1. Guideline working group

This guideline was developed and solely sponsored by The European Society of Endocrinology (ESE), supported by CBO (Dutch Institute for health care improvement). The working group was chaired by Jens Bollerslev (clinical) and Olaf Dekkers (methodology) and included Claudio Marcocci, Lars Rejnmark, and Dolores Shoback (endocrinologists), Wim van Biesen (nephrologist), and Antonio Sitges Sierra (endocrine surgeon). The working group had two in-person meetings (January and December, 2014) and communicated by phone and email. Consensus was reached upon discussion, minority positions were taken into account in the rationale behind recommendations. Prior to the process, conflict of interest forms were completed by all participants.

2.2 Target group

This guideline was developed for European based healthcare providers of adult patients with chronic HypoPT, ie, primarily endocrinologists and specialists in internal medicine. However, general practitioners with a special interest in calcium metabolism might also find the guideline useful, as might our patients. Patient leaflets were developed in collaboration with patients and patient associations (xxx, xxx, and xxx) based on the guideline recommendations. A draft of the guideline was reviewed by an expert in the field, before submitted for external review and comments by ESE-members, and was presented and discussed at the European Congress of Endocrinology, May 18th, 2015 in Dublin.
2.3 Summary of Methods used for guideline Development

The current guideline has the GRADE (Grading of Recommendations Assessment, Development and Evaluation) principles as methodological base. GRADE is a systematic approach for synthesizing evidence and grading of recommendations (1). The main advantage of the system is the aim for transparency at all stages of the guideline development process. This to provide the reader with all information required to understand the underlying rationale of the provided recommendations.

The first methodological step for the guideline development group is to define the clinical question(s) to be addressed in the guideline (see section 2.4). These clinical questions are formulated in such ways that their answering can directly inform management decisions. An answer to the question: What is the best treatment in HypoPT to prevent renal complications, can inform treatment decisions. Whereas the question: Is hydrochlorothiazide better than PTH for treatment in HypoPT to prevent renal complications, is too restricted if other alternatives are available but not considered. Importantly, the clinical questions should be specific in terms of populations; for this guideline: chronic HypoPT in adults who do not have end-stage renal disease. Prior to synthesizing and rating available evidence, the guideline development group rated clinical outcomes either as critical, important but non-critical, and not important (2), see Section 2.4.

The clinical questions subsequently formed the base for a systematic literature search, see Section 2.5. After including all relevant articles, synthesis of the evidence was made in two directions: 1) Estimation of an average effect for specific outcomes (if possible): 2) Rating the quality of the evidence. The quality rating is standardized (3) and is provided as summary rating (using four categories: high, moderate, low, very low) across studies for each outcome, as it may be that quality differs for different outcomes. See the evidence tables in Appendix 1.

Evidence synthesis and quality rating were performed by the guideline methodologist.

For the final recommendations, three elements importantly were taken into account: 1) Quality of the evidence, 2) Balance of desirable and undesirable outcomes, 3) Values and preferences (patient preferences, goals for health, costs, management inconvenience, feasibility of implementation, etc) (4). The recommendations are worded as recommend (strong recommendation) and suggest (weak recommendation). The meaning of a strong recommendation can be stated as follows: reasonably informed persons (clinicians, politicians, patients) would want the management in accordance with the recommendation. For a weak recommendation, most persons would still act in accordance with the guideline,
but a substantial number would not (4). Only for recommendations regarding treatment we
aimed for formal evidence synthesis; this was not the case for recommendations on diagnosis,
monitoring and special circumstances.

Importantly, there is no automatic step from evidence to recommendations. Often available
evidence is of poor quality hampering strong recommendations, but even high quality
evidence may not directly translate into a strong recommendation if, for example, the outcome
under study is judged as not important or if a management strategy cannot be implemented on
a large scale. This highlights the fact that standardized quality judgement still does not
eliminate the need for clinical judgement (1). Another consideration is that you cannot abstain
from recommendations when there is no evidence, as treatment decisions need to be made any
way. For the ESE guidelines, recommendations are achieved by majority reports of the
guideline development committee, but if members have substantive disagreements, this will
be acknowledged in the manuscript. To optimize transparency, all recommendations provided
are accompanied by text explaining why specific recommendations were made.

2.4. Clinical question, eligibility criteria and endpoint definition

The clinical question on which the literature search was based and for which available
evidence was synthesized was: What is the best treatment for adult patients with chronic
HypoPT?

Exclusion criteria for the studies considered were:
- Patients with HypoPT for < 6 months
- Intervention < 4 week duration
- Age < 18 years
- Case series
- End-stage renal disease

The following outcomes were rated by the guideline working group as critical:
- Mortality
- Quality of life
- Calcium levels in serum or plasma and urine, including incidence of hypercalcaemia
- Chronic kidney disease and renal calcifications defined as symptoms or episodes of
  nephrolithiasis or nephrocalcinosis
- Cramps, tetany and seizures
Cardiovascular disease defined as the incidence of major adverse cardiovascular events

Disability or sick leave

2.5 Description of search and selection of literature

A systematic search was done using the database Ovid MEDLINE to find literature from 1970 onward. Systematic reviews, randomized controlled trials (RCTs), cohort studies and case-control studies were eligible; only articles in Dutch, English, German and French were considered. Articles were searched that included adult, human patients with chronic HypoPT (>6 months) as well as the relevant interventions and outcome measures. Only interventions with duration > 4 weeks were considered. Articles identified by the working group as relevant were used to optimize the search strategy. Articles found by “snowballing” were also considered. For the full search strategy, see Appendix 2.

This systematic search found 1,100 articles, reduced to 312 based on title and abstract. The working group members assessed 312 articles for eligibility in more detail, of which 32 articles were assessed in full-text. One article (5) could not be located in full-text and was excluded. The final literature selection included 16 articles. Of note, for the final recommendations also other literature (basic literature, physiologic studies) was also taken into account.

3. Clinical considerations in Chronic Hypoparathyroidism

3.1 Etiology and epidemiology

HypoPT is an endocrine disease with low calcium and inappropriately low (insufficient) circulating parathyroid hormone (PTH) levels (6-9). It is a rare condition, designated as an orphan disease by the European Commission in January, 2014, (EU/3/13/1210) http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/orphans/2014/01/human_orphan_001301.jsp&mid=WC0b01ac058001d12b and the only major endocrine condition today, where the hormonal insufficiency in general is not treated by substitution of the missing hormone (PTH). The most common cause of chronic HypoPT is neck surgery i.e., secondary to thyroid or parathyroid surgery (10), but the disease also has an autoimmune basis (11) and/or a genetic etiology, like DiGeorge syndrome (12).

The prevalence of postsurgical HypoPT has recently been systematically studied in Denmark, where a total of more than 2000 patients were identified giving a prevalence of approximately
24/100,000 inhabitants, among whom only a minority (2/100,000) had HypoPT due to non-surgical causes (13;14). These estimates are in agreement with recent data from USA, showing a prevalence of the same magnitude for patients with chronic HypoPT (15).

3.2 Postsurgical Hypoparathyroidism

Chronic HypoPT in adults of more than 6 months duration is usually secondary to previous thyroid surgery, but may also occur following parathyroidectomy or other cervical surgical procedures. Completion thyroidectomy (after previous partial thyroidectomy) or lymph node dissection of the central neck compartment for locally recurrent cancer may also lead to HypoPT. Overall, between 2-10% of patients submitted to total thyroidectomy (often associated with central/lateral lymph node dissection in cases of thyroid cancer) will develop chronic HypoPT (16).

The initial manifestation of postoperative parathyroid failure is hypocalcaemia detected within 24 hours of thyroidectomy, which occurs in 30-60% of patients undergoing total thyroidectomy. Predisposing factors involved are young age, female gender, Graves’ disease, lymphadenectomy, accidental parathyroidectomy (including biopsies during surgery for hyperparathyroidism), parathyroid auto-transplantation and, most importantly, the number of functioning parathyroid glands remaining in situ (17;18). All these factors contribute to reduced PTH secretion immediately after surgery resulting in hypocalcaemia (19;20). If hypercalcaemia was present prior to surgery (e.g., in a patient with hyperparathyroidism), it may take a few days before serum calcium levels have normalized, during which PTH levels may be very low.

About 60-70% of cases of postoperative hypocalcaemia resolve within four to six weeks after surgery (transient HypoPT); the rest will progress to protracted HypoPT characterized by low serum PTH levels and the need for continued treatment. The most relevant factor leading to protracted HypoPT is the number of functioning parathyroid glands remaining in situ; clinical and disease-related variables lose significance at this stage (21).

Finally, about 15-25% of patients with protracted HypoPT will develop chronic HypoPT. The significant variables favouring recovery from protracted HypoPT are the number of parathyroid glands remaining in situ and the serum calcium level at this stage: Normal to high calcium levels at one month after thyroidectomy appears to increase the chance of parathyroid gland recovery. The clinical and disease-related variables do not seem to influence parathyroid function recovery. The risk of chronic HypoPT is closely related to the number of
parathyroid glands remaining in situ at operation: 16% for cases with 1-2 preserved glands, 6% for 3 glands and 2.5% for 4 glands (21).

3.3 Complications and Renal Implications of Chronic Hypoparathyroidism in Adults

Patients with chronic HypoPT seem to have lower quality of life (QoL), muscle complaints, including fatigue and weakness, more anxiety and tendency to depression (22-25). In support of these issues, large cohort studies from Denmark have shown increased risk of hospitalization for depression and affective disorders, renal impairment, and infections, whereas the risk for cancer and overall mortality was not increased (13;26). Risks of ischemic heart disease and of cataract are increased in non-surgical HypoPT, but not among patients with postsurgical HypoPT (13;14;26).

HypoPT has traditionally been associated with calcium-containing urolithiasis and renal impairment, because of an increased calcium-phosphate product. Loss of renal PTH action decreases renal tubular reabsorption of calcium and excretion of phosphate causing hypercalciuria and hyperphosphataemia, respectively (9). Thus, patients with chronic HypoPT have been found to have an increased risk of renal complications, such as renal stones, renal insufficiency and a higher risk for needing dialysis (13). Impaired renal function has been associated with age of the patient, duration of the disease, and relative time with hypercalcaemia (27). In agreement, two smaller cross-sectional studies in patients with mainly postsurgical HypoPT have found renal complication rates in the same magnitude (22;28). Moreover, two thirds of subjects included in an early intervention trial had decreased creatinine clearance values at baseline, and 40% had verified renal calcinosis (29). However, despite keen interest in improving the management of HypoPT, large cohort studies describing typical treatment patterns, optimized target laboratory parameters and rates of complications are scarce.

3.4 Pregnancy and breastfeeding

Pregnancy and lactation pose substantial short-term challenges to maternal calcium homeostasis, due to the need to mineralize the fetal skeleton and to provide this essential mineral to the breast milk to sustain postnatal skeletal development and well-being in the newborn (30-34). These challenges to the mother are met by vigorous placental production of 1,25-dihydroxyvitamin D (1,25(OH)₂D), which stimulates intestinal calcium and phosphate absorption during pregnancy, resulting in higher levels of urinary calcium and low to suppressed endogenous PTH secretion. As pregnancy progresses, parathyroid hormone-related protein (PTHrP) production increases in many tissues. PTHrP synthesis rises even further during nursing, because it is abundantly produced in lactating mammary tissue.
PTHrP increases bone resorption substantially and renal calcium reabsorption, which together provides a steady supply of calcium for milk production. PTHrP’s effects on the kidney prompt urinary calcium levels to fall during lactation. Because of the changes in PTHrP and 1,25(OH)₂D during pregnancy and lactation, levels of endogenous PTH are suppressed. Although PTH plays a negligible role in regulating calcium homeostasis in pregnancy and lactation in normal women, those with chronic HypoPT, whose serum calcium levels are being maintained by supplemental calcium intake and therapy with vitamin D metabolites or analogues, are at considerable risk for both hypercalcaemia and hypocalcaemia when pregnant or nursing. Poor control of maternal HypoPT and resulting hypocalcaemia during pregnancy can cause miscarriage, stillbirth, premature labor and even neonatal death (34-37). Maternal hypocalcaemia can affect neonatal skeletal development and cause compensatory hyperparathyroidism in the newborn. Skeletal deformities, fractures, parathyroid hyperplasia, and clinical complications (e.g., respiratory distress, poor feeding, hypotonia) may result (32;34-41). Conversely, maternal overtreatment resulting in hypercalcaemia can suppress fetal parathyroid development causing neonatal hypocalcaemia. To avoid these potential complications, pregnant and nursing women with HypoPT need careful monitoring and medication adjustment by their physicians. The clinical literature on which summary is based is detailed in Appendix 4.

### 3.5 Treatment

The aim of treatment of chronic HypoPT is to relieve symptoms of hypocalcaemia and improve the patient’s QoL (9;42). The treatment should aim to maintain serum calcium levels in the low normal range, serum phosphate within the normal range, total calcium-phosphate product below 4.4 mmol²/L² (55 mg²/dL²), and to avoid hypercalciuria.

Standard treatment includes oral calcium salts and active vitamin D metabolites. Hyperphosphataemia should be addressed by decreasing dietary phosphate intake and by eventually using phosphate binders (9;42;43). In the event of hypercalciuria, a thiazide diuretic accompanied by a low salt diet may be advised (44). Replacement therapy with PTH (synthetic human PTH₁-34 and intact PTH₁-84) is an attractive option for those patients who do not stably and safely maintain their serum and urinary calcium in the target range (43;45). Both compounds have shown to be effective (43) and the American Food and Drug Administration has very recently approved the use recombinant human PTH₁-84 as a supplement to conventional treatment (FDA 2015: [http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm431358.htm](http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm431358.htm)).
Patients with mild hypocalcaemia should be given oral therapy even if they have only nonspecific symptoms (fatigue, brain fog, anxiety), since they may improve with treatment. Dietary calcium intake should be optimized, according to the guidelines for the general population (46,47). Magnesium-depleted patients should be replete with this mineral.

In cases of symptomatic severe hypocalcaemia, the use of intravenous calcium should be considered for a limited period of time. Serum calcium and phosphate should be monitored weekly or twice weekly during the initial dose adjustment period and every third to sixth month when serum levels are stable. 24-hour urinary calcium excretion is suggested to be measured yearly or every other year.

The overall purpose of this guideline is to provide clinicians with guidance on the treatment of chronic HypoPT. We intended to draft a practical clinical guideline, focusing on operationalized recommendations that are supposed to be useful in the daily management of adult patients with chronic HypoPT.

5. Conclusions from scientific literature and directions for further research

5.1 Summary and interpretation of the main findings

Sixteen studies on treatment on chronic HypoPT were included based on eligibility criteria and endpoint definition (see 2.5). Only one study (48) had a sample size of > 100 patients.

Most of the (few) available randomized studies investigated effects of PTH replacement therapy. Details of included studies are shown in appendix 1. A more extensive summary, the formal conclusions, and the GRADE scoring per endpoint and evidence synthesis are provided in appendix 2 and 3.

Study endpoints

Mortality

Only one study reported data on mortality (48). No deaths were reported in this randomized study with 134 patients comparing PTH to placebo. The follow-up was short (24 weeks), not allowing conclusions regarding long-term effects on mortality.

Quality of life, disability and sick leave

In two studies QoL was studied. Whereas a cohort study showed improvement in QoL compared to baseline after treatment with PTH (49), an advantage in QoL of therapy with PTH compared to placebo could not be shown in a RCT (50). No studies reported on disability or sick leave.
Cardiovascular events

Two studies (25;48) reported one serious cardiovascular event in the PTH-treated group, compared to none in the placebo group. Sample sizes were too small and follow-up too short to draw meaningful conclusions regarding cardiovascular events.

Cramps, tetany and seizures

Occurrence of cramps, tetany or seizures was not quantitatively reported in the majority of studies. In one RCT the reported frequency of tetany did not differ materially between PTH and placebo group (48).

Renal function, kidney stones and calcifications

Although nephrocalcinosis or nephrolithiasis is described in HypoPT, no study adequately investigated the occurrence of these conditions under different treatment regimens.

Serum and urinary calcium levels

Many studies reported in various ways on serum calcium levels. In general, calcium levels within the target range can be achieved with different treatment (combinations), and the risk of severe hypo- or hypercalcaemia is low.

5.2 Study results in perspective

Very little evidence is available on how best to treat HypoPT. Data on QoL and the risk of complications have just started to emerge in recent years, and clinical trials on how to optimize therapy are essentially non-existent. Importantly, the majority of studies are of limited sample size, which hampers firm conclusion especially regarding dichotomous outcomes (mortality, cardiovascular events). Also no studies are available that relate target calcium levels to clinical relevant endpoints. Thus, we do not know what the optimal calcium target is. Because of this remarkable lack of data, it is not possible to formulate recommendations based on strict evidence. This ESE guideline on treatment of chronic HypoPT in adults is, therefore, mainly based on how patients are managed in clinical practice, as reported in small case series and based on the experiences of the authors of the guideline.

Noticeably, HypoPT is one of the last endocrine deficiency diseases not treated by hormone replacement. In recent years, a number of studies have been published showing that normocalcaemia can be maintained with PTH (rhPTH1-84) or a PTH fragment (rhPTH1-34). In most of the studies, PTH has been administered in an unphysiologic manner (once-daily injection), compared to its continuous episodic endogenous pattern of secretion. Due to the short plasma half-life of PTH, once-daily injections do not cause sustained increased PTH levels. In other words, the physiology of calcium-phosphate homeostasis is not restored by
this schedule of replacement therapy. Recently, a National Institutes of Health (NIH) sponsored study in the USA showed an almost normalization of the diurnal rhythm of PTH, calcium and phosphate levels in response to rhPTH therapy delivered by an (insulin) infusion pump (51). So far, no data are available on whether continuous infusions of rhPTH will improve QoL and reduce the risk of complications. If so, this may be a feasible way forward to improve the treatment of chronic HypoPT in adults. As HypoPT recently has been acknowledged as an orphan disease in Europe and the USA, further systematic and prospective studies on how to optimize therapy and avoid complications will hopefully be initiated.

6. Recommendations, Rationale for the Recommendations

6.1. Diagnosis

6.1.1 We recommend considering a diagnosis of HypoPT in a patient with hypocalcaemia and inappropriately low PTH levels.

Reasoning:

Hypocalcaemia is defined as an ionized or albumin adjusted serum total calcium level below the lower limit of the reference interval. Measurements of ionized or total calcium mostly reflect local traditions, however, ionized calcium measurements might improve diagnostic accuracy (52), and is preferred in pregnancy, see 6.5.3. A specific cut-off limit for PTH levels in the presence of hypocalcaemia cannot be defined. If parathyroid function is intact, hypocalcaemia is normally associated with (markedly) increased PTH levels (secondary hyperparathyroidism). In accordance, a diagnosis of HypoPT may be considered in a patient with hypocalcaemia even though PTH levels are within the reference interval (inappropriate normal PTH levels) (6-9).

Remarks

Magnesium depletion impairs the secretion of PTH causing a state of “functional HypoPT” and impairs effective PTH actions in target tissues. If magnesium levels are low, this should be corrected before diagnosing a patient with chronic HypoPT (53).

6.1.2 We suggest considering genetic testing and/or family screening in a patient with HypoPT of unknown etiology.

Reasoning:

Non-surgical HypoPT may be due to various reasons (43;54). If no obvious cause can be established, we suggest considering genetic testing and/or family screening. This may be of
specific importance to younger individuals, as a genetic diagnosis may allow for genetic
counseling in relation to pregnancy plans and for monitoring for other possible complications
that may accompany the HypoPT (e.g., renal and hearing abnormalities due to GATA3
mutation).

6.2. Goals of management in chronic hypoparathyroidism

6.2.1 We suggest treatment targeted to maintain calcium level (albumin adjusted total
calcium or ionized calcium) in the lower part or slightly below the lower limit of the reference
range (target range) with patients being free of symptoms or signs of hypocalcaemia.

Reasoning:
No data exist on optimal serum calcium levels during treatment of HypoPT. Aiming at low
normal or slightly below the lower limit of normal for serum calcium levels seems reasonable,
as this may help to lower renal calcium excretion and avoid risk of hypercalcaemia (55).
Some patients may, however, need higher serum calcium levels to be free of symptoms. If the
patient’s well-being is improved by titrating treatment in such a manner that serum calcium
levels are in the upper part of the reference interval, this may be accepted as no data exist on
whether relatively high normal serum calcium levels are of specific harm to patients.

6.2.2 We suggest that 24-hour urinary calcium excretion should be within reference range.

Reasoning:
In a patient with intact parathyroid function, hypercalciuria is considered a risk factor for
renal stone formation. Because PTH increases the renal tubular reabsorption of calcium,
chronically low PTH levels make hypercalciuria a common feature of HypoPT. Risk of renal
stone disease is increased in HypoPT (13;27), but no evidence exists as to whether the risk of
forming or passing renal stones is associated with the amount of urinary calcium excreted in
patients with HypoPT. However, if it is assumed that the pathogenesis of renal stone disease
is similar in HypoPT as in hypercalciuric individuals with normal parathyroid function, it
seems reasonable to aim at keeping 24-hour urinary calcium within the sex-specific reference
range (55) in order to prevent renal stone formation (56).

Remark
If sex-specific reference ranges are available we suggest using them, as the urinary calcium
excretion in higher in men compared to women.

6.2.3 We suggest that serum phosphate levels should be within the reference range.

6.2.4 We suggest that the serum calcium–phosphate product should be below 4.4 mmol²/L²
(55 mg²/dL²).

Reasoning:
HypoPT is characterized by a relatively high serum phosphate level and a higher than normal calcium-phosphate product. This is attributable to the lack of the phosphaturic effect of PTH, as well as an increased intestinal absorption of phosphorus due to activated vitamin D treatment (9;27;43). Risk of extra-skeletal calcifications, including nephrocalcinosis and cataract, is increased in HypoPT. It is generally assumed that this is related to high serum phosphate levels and an increased serum calcium-phosphate product, why it seems reasonable to aim at keeping phosphate levels within the normal range (57).

6.2.5 We suggest that serum magnesium levels should be within the reference range.

Reasoning:
Magnesium is central for several physiological processes, including secretion and actions of PTH. Low magnesium levels may cause functional HypoPT by blunting the (residual) capacity of the parathyroid glands to secrete PTH (58). Moreover, low magnesium levels may cause symptoms similar to hypocalcaemia. Accordingly, it seems reasonable to aim at keeping serum magnesium levels within the reference range.

6.2.6 We suggest aiming at an adequate vitamin D status.

Reasoning:
Vitamin D insufficiency has been associated with adverse effects on skeletal as well as extra-skeletal health (59). Severe vitamin D deficiency is associated with symptoms of myopathy, and patients with HypoPT often have neuromuscular complains (9;43;50). To ensure that symptoms are not caused by low vitamin D levels, it seems reasonable to ensure an adequate vitamin D status (53). A serum concentration of 25-hydroxyvitamin D (25OHD) between 75-125 nmol/L (30 – 50 ng/mL) may be considered as adequate (60).

Remarks:
Treatment with activated vitamin D analogues does not ensure an adequate vitamin D status in terms of serum 25-hydroxyvitamin D levels. As calciferol itself may be of importance to a number of cellular processes and may undergo hydroxylation to 1,25(OH)2D catalyzed by local hydroxylases in different tissues (61), it seem reasonable to ensure sufficient 25OHD levels, despite treatment with activated vitamin D analogues.

6.2.7 We recommend to personalize treatment and focus on the overall well being and QoL of the patient when implementing different therapeutic efforts, aiming to achieve the therapeutic goals.

Reasoning:
The therapeutic goals (albumin adjusted serum calcium levels 2.1 - 2.3 mmol/L or S-Ca2+ levels 1.10 – 1.25 mmol/L) are mainly based on reasoning according to normal physiology,
assuming that normalization of biochemical indices may be advantageous to patients. However, it has to be emphasized that no firm evidence exists on long-term benefits (or harms) of achieving these therapeutic goals. Accordingly, patients cannot be ensured long-term beneficial effects, when accepting potential side-effects to drug treatment or (troublesome) changes in lifestyle (dietary habits). Thus, we consider it inappropriate management, if therapeutic efforts have immediate negative impact on a patient’s well-being or QoL.

6.2.8 We recommend providing information/education that enables patients to know the possible symptoms of hypo- or hypercalcaemia and/or complications to their disease.

Reasoning:

As stated in Section 6.4, we suggest monitoring of patients at regular time intervals. Serum calcium levels may, however, change, and complications may emerge at any time, with or without any apparent reasons. Thus, we find it of importance to empower patients with knowledge of symptoms and co-morbidities and drugs that may be related to changes in the course of their disease.

Table 1 shows typical symptoms of hypo- and hypercalcaemia, which patients should be informed of.

Table 2 shows co-morbidities which may occur with an increased prevalence in HypoPT.

Table 3 list drugs, conditions and diseases which may interfere with calcium homeostasis. If a patient is diagnosed with one of the diseases or initiates treatment with one of the drugs, this may necessitate changes in the medical treatment of HypoPT in order to maintain normocalcaemia.

6.3. Treatment

6.3.1 We recommend treatment of all patients with chronic HypoPT with symptoms of hypocalcaemia and/or an albumin adjusted serum calcium level < 2.0 mmol/L (< 8.0 mg/dL / ionized serum calcium (S-Ca\(^{2+}\)) levels < 1.00 mmol/L).

6.3.2 We suggest offering treatment to asymptomatic patients with chronic HypoPT and an albumin adjusted calcium level between 2.0 mmol/L (8.0 mg/dL / S-Ca\(^{2+}\) 1.10 mmol/L) and the lower limit of the reference range in order to assess whether this may improve their well-being.

Reasoning:

In chronic HypoPT, symptoms of hypocalcaemia may vary widely, from an asymptomatic state to life-threatening conditions, such as seizures, cardiac failure, bronchospasm and laryngospasm etc. (7;9;27;43). While it is obvious to recommend treatment of patients with
severe symptoms of hypoalcaemia, no evidence exists on whether asymptomatic patients with biochemical hypoalcaemia should be treated. No limit of serum calcium levels have been defined below which, treatment is unquestionably needed. Symptoms of hypoalcaemia do not translate directly to serum calcium levels. Sudden fluctuations in serum calcium levels may cause symptoms, even if calcium levels are (almost) normal. On the other hand, no apparent symptoms may be present, despite low calcium levels, if the hypoalcaemia has developed slowly. In a patient with intact parathyroid function, serum calcium levels are tightly regulated within a narrow range (62;63). It seems likely that patients with no complaints of hypoalcaemia, despite (very) low serum calcium levels, have adapted to a new calcium homeostasis which may have blunted their hypoalcaemic symptoms. We, therefore, consider it reasonable to offer treatment to asymptomatic patients with chronic HypoPT, since treatment might improve their well-being (Figure 1). If no improvements occur following 6-12 months of therapy, the need for treatment may be reconsidered, especially if hypoalcaemia is only mild. However, vitamin D levels should be optimised.

6.3.3 We recommend the use of activated vitamin D analogues plus calcium supplements in divided doses as the primary therapy.

6.3.4 If activated vitamin D analogues are not available, we recommend treatment with calciferol (preferentially cholecalciferol).

6.3.5 We recommend that the doses of activated vitamin D analogues or cholecalciferol are titrated in such a manner that patients are without symptoms of hypoalcaemia and serum calcium levels are maintained within the target range.

Reasoning:

No evidence exists from direct comparisons within clinical trials as to the best way to treat HypoPT. Prior to the development of activated vitamin D analogues, calciferol (ergocalciferol [vitamin D2] or cholecalciferol [vitamin D3]) was used in the treatment of HypoPT and supraphysiological doses of calciferol (typical 25,000 – 200,000 IU/day) were needed to maintain normocalcaemia, usually resulting in very high plasma concentrations of 25OHD (typically 500-1000 nmol/l). Following the development of activated vitamin D analogues, small case-series showed that normocalcaemia could be achieved in HypoPT treated with activated vitamin D analogues (64;65). Today, activated vitamin D analogues are preferred due to a shorter plasma half-life, allowing for dose titration at shorter time-intervals compared with calciferol. Moreover, in case of intoxication, serum calcium levels will normalize faster if patients are treated with activated vitamin D analogues (66;67).
Either alfacalcidol (1α-hydroxyvitamin D) or calcitriol (1,25(OH)₂D) may be used. Effects of the different analogues have not been compared head-to-head in HypoPT. In terms of calcaemic effects, calcitriol is approximately twice as potent as alfacalcidol. To maintain serum calcium levels within the target range, the daily dose must be carefully titrated, as the dose needed varies between patients. Daily doses of calcitriol are typically 0.25 to 2.0 μg, equal to a daily dose of 0.5 to 4.0 μg of alfacalcidol (68).

If serum calcium levels are slightly outside the target range, or a patient is complaining of symptoms, the daily dose of activated vitamin D analogue may be gradually changed (Figure 1) i.e., daily dose of alfacalcidol may be changed by 0.5 (or 0.25) μg corresponding to a 0.25 μg change in dose of calcitriol. Larger changes in dose may be needed in case of severe hypo- or hypercalcaemia. In order to allow for a new steady-state, dose adjustments should (if possible) not be performed more frequently than at 2-3 days’ time intervals (69). If only minor symptoms or biochemical disturbances are to be adjusted, weeks may be allowed to pass between dose adjustments. If a patient is on treatment with high doses of calciferol, 2-3 months are needed between dose adjustments, before a new steady state has emerged.

Intake of calcium from supplements (or diet) causes only a relatively transient increase in serum calcium levels. Extra intake of calcium may be recommended pro re nata (PRN) if a patient is only experiencing symptoms of hypocalcaemia once in a while.

**Calcium intake:** An adequate daily intake of calcium from diet and supplements is advisable.

Intake of calcium from dietary sources (mainly dairy products) is considered equivalent to intake from supplements (70). Patients with HypoPT are most often recommended to use calcium supplements in a total daily dose of 800-2000 mg of elemental calcium, although sometimes higher doses are used. The absorptive capacity of the intestine is probably saturated by intake of a dose of approximately 500 mg of calcium in one ingestion. Thus, a higher amount per dose is unlikely to be of benefit to the patient (71;72). Accordingly, intake of calcium should be divided into smaller doses and spread throughout the day. Different calcium salts are available as supplements. Calcium carbonate is most often used and less expensive than other calcium preparations. However, calcium carbonate requires an acidic environment for absorption and should, therefore, be taken together with a meal (70). Calcium citrate should be recommended to patients with achlorhydria or on treatment with proton pump inhibitors (PPI), as well as to patients who preferred to take supplements outside mealtimes (72).
A high intake of calcium from diet and supplements may lower the dose of vitamin D needed to maintain serum calcium levels within the target range. It is unknown whether a relatively high intake of calcium from supplements (> 1000 mg/d) is of advantage, as it may cause hypercalciuria. On the other hand, calcium binds phosphorus in the intestine and may thereby lower plasma phosphate levels (73). Thus, in selected cases high doses of calcium supplement may be needed.

6.3.6 We recommend vitamin D supplementations in a daily dose of 1000-2000 IU to patients treated with activated vitamin D analogues.

Reasoning:
In order to ensure an adequate vitamin D status, a daily cholecalciferol dose of 1000-2000 IU (25-50 µg) will most likely ensure a serum 25OHD level within the suggested target range of 75-125 nmol/L (30 – 50 ng/mL), Figure 1.

6.3.7 In a patient with hypercalciuria, we suggest considering a reduction in calcium intake, a sodium-restricted diet, and treatment with a thiazide diuretic.

Reasoning:
In HypoPT, the risk of renal complications is increased (13;27;43), but no data are available on whether a high renal calcium excretion is associated with the increased risk. However, as HypoPT causes pathological high renal calcium excretion it is reasonable to aim to normalize the 24-hour urinary calcium, Figure 1.

No data exist on whether dietary recommendations are useful in reducing urinary calcium in HypoPT. In patients with intact parathyroid function, urinary calcium is positively associated with intake of calcium and sodium (74;75). Accordingly, it may be helpful to reduce the intake of sodium (Figure 1). If patients are on treatment with a high daily dose of calcium supplements, daily dose of (activated) vitamin D may be increased in order to allow for a reduced dose of calcium supplements.

If dietary recommendations or changes in the daily dose of calcium supplements and/or activated vitamin D analogue do not reduce urinary calcium, treatment with a thiazide diuretic may be considered, Figure 1. Thiazide diuretics have been shown to reduce urinary calcium in patients with HypoPT (44;76-79). By lowering renal calcium excretion, thiazides may exert a calcium-sparing effect, allowing for reduced doses of calcium supplements. Addition of amiloride to treatment with a thiazide may further lower urinary calcium losses and decrease the risk of hypokalemia. Moreover, amiloride may lower renal magnesium excretion (80). However, no data are available on whether thiazides reduce risk of renal complications in HypoPT.
If a thiazide diuretic is prescribed, it should be noted that the hypocalciuric effect is dose-dependent, and treatment should preferably be combined with sodium restriction (81). A relatively high dose administered twice a day is often needed in order to lower 24-hour urinary calcium i.e., hydrochlorothiazide 50 mg twice daily or bendroflumethiazide 5 mg twice daily. Thiazide-like diuretics (e.g., chlorthalidone and indapamide) may, however, be administered only once daily as they have a longer duration of action.

Risk of side-effects increases with dose, and potential side-effects should be monitored closely during treatment, including blood electrolyte disturbances and blood pressure.

6.3.8 In a patient with renal stones, we recommend evaluation of renal stone risk factors and management according to relevant international guidelines.

Reasoning:

Although calcium-containing stones are likely to be the most frequent type of stones in HypoPT, patients with renal stones should receive a full evaluation of possible causes, and treatment should be advised according to relevant guidelines (82;83), Figure 1.

6.3.9 In a patient with hyperphosphataemia and/or an elevated calcium-phosphate product, we suggest considering dietary interventions and/or adjustment of treatment with calcium and vitamin D analogues.

Reasoning:

As high serum phosphate levels and/or a high calcium-phosphate product are presumed to increase risk of extra-skeletal calcifications, interventions aiming at normalizing these biochemical indices may be considered (84) (Figure 1), although evidence from trials are lacking. Patients may be advised to reduce intake of dietary sources rich in phosphate. As calcium binds phosphate in the intestine and calcitriol increases intestinal absorption of phosphorous, it may be considered to titrate therapy so that the daily dose of calcium supplements is increased, which may allow for a decrease in daily dose of activated vitamin D analogue. Following such changes, 24-hour urinary calcium should be measured in order to ensure that patients have not developed severe hypercalciuria. No data exist on use of phosphate binders in HypoPT. Of notice, however, recent studies in patients with chronic kidney diseases (mostly not on dialysis) have suggested an increased mortality and risk of vascular calcifications in those on treatment with calcium-containing vs. calcium-free phosphate binders (85). It is unknown whether lowering phosphate levels in HypoPT by increasing calcium intake is of benefit or harm to patients, which is why no firm recommendation can be stated on this matter.
6.3.10 In a patient with hypomagnesaemia, we suggest considering measures that may increase serum magnesium levels.

**Reasoning:**

Low magnesium levels are often reported in HypoPT. In addition to HypoPT as an explanation for hypomagnesaemia, other causes should be considered such as treatment with diuretics and PPI (86). In order to normalize magnesium levels, treatment with magnesium supplements or amiloride may be considered (80;87), Figure 1.

Magnesium supplements are, however, not always well tolerated due to gastrointestinal adverse events.

In addition to lowering renal potassium excretion, amiloride has also been shown (in patients with an intact parathyroid function) to work as a magnesium-sparing diuretic (24).

If magnesium levels are chronically low, a magnesium infusion test (0.5 mmol of magnesium per kg of body weight, in a saline solution of 500 mL, administered as an intravenous infusion over 6 hours) may be considered. If renal function is mildly impaired, the dose should be reduced. If renal function is severely impaired, this test should not be done. The results of this test will provide information on whether the patient has intracellular magnesium depletion. If 24-hour urinary magnesium excretion is < 50% of the amount infused, this signifies magnesium depletion, and the infusion itself will treat the magnesium deficiency (88).

6.3.11 We recommend against routine use of replacement therapy with PTH or PTH analogues

**Reasoning:**

Normocalcaemia can be achieved in response to subcutaneous injections with intact PTH or the N-terminal fragment of PTH (PTH$_{1-34}$; teriparatide) (25;29;48). Treatment with PTH reduces the dose of activated vitamin D analogues and calcium supplements needed to remain at target levels of biochemical indices. However, long-term beneficial effects have so far not been shown in RCTs examining other outcomes such as hypercalciuria, renal complications, or QoL (29;48;50). A markedly improved well-being has, nevertheless, been reported in response to PTH therapy in case reports and in sub-groups of patients included in trials on PTH therapy (29;49;89). Accordingly, it is possible that PTH therapy may be of benefit for certain patients.

**Remarks**

Injection therapy with PTH is currently not marketed for the treatment of HypoPT in Europe. Recombinant human intact parathyroid hormone (rhPTH$_{1-84}$) (Natpara®, Shire) has recently been approved by the U.S. Food and Drug Administration for long-term treatment of
HypoPT. Marketing authorization application for rhPTH$_{1-84}$ has been submitted to the European Medicines Agency.

### 6.4. Monitoring

#### 6.4.1 We recommend routine biochemical monitoring of serum levels ionized or albumin adjusted total calcium, phosphate, magnesium and creatinine (eGFR), as well as assessment of symptoms of hypocalcaemia and hypercalcaemia at regular time intervals (e.g., every 3-6 months).

**Reasoning:**

In a patient with HypoPT on stable therapy, serum calcium and renal function may change without obvious causes and without causing noticeable symptoms. Although no data exist on how best to monitor patients with HypoPT, it seems reasonable to offer biochemical screening to patients at regular time intervals, Figure 1.

As no straightforward relationship exists between serum calcium levels and hypocalcemic symptoms, occurrence of hypocalcemic symptoms should also be assessed at regular time intervals, in order to assure that the treatment provides relief of symptoms, without causing side-effects.

#### 6.4.2 Following changes in therapy, we recommend biochemical monitoring weekly or every other week.

**Reasoning:**

If the daily dose of activated vitamin D or calcium is changed or if new drug treatment is introduced (such as thiazide diuretics), serum levels of calcium, phosphate, magnesium and creatinine (eGFR) should be closely monitored for the first weeks, Figure 1. In case of severe hypo- or hypercalcaemia, more frequent monitoring (several times a week) may be needed.

#### 6.4.3 We suggest considering monitoring of 24-hour urinary calcium excretion at regular time intervals (e.g., once a year or every second year).

**Reasoning:**

As hypercalciuria is considered a risk factor for renal calcifications, assessment of 24-hour urinary calcium at regular time intervals may allow for early intervention if hypercalciuria is present. No data are, however, available on whether this will help to reduce long-term morbidity.

#### 6.4.4 We recommend renal imaging if a patient has symptoms of renal stone disease or if serum creatinine levels start to rise.

**Reasoning:**
Risks of renal complications are significantly increased in HypoPT (13). Deterioration of renal function, as detected by increased creatinine levels, or symptoms compatible with renal stone disease should be carefully investigated, Figure 1. It is unknown whether screening for renal calcifications by use of routine renal imaging at certain time intervals is advantageous.

6.4.5 We suggest monitoring for development of signs or symptoms of co-morbidities at regular time intervals (e.g., yearly).

Reasoning:
HypoPT is associated with a number of co-morbidities (Table 2). Early detection of such complications may be of importance which is why it seems reasonable to assess, in a systematic manner, whether patients are experiencing symptoms which may indicate emerging complications. Of note, no study in patients with HypoPT has shown the beneficial effect of screening for these co-morbidities.

As certain drugs/diseases and conditions may interfere with the treatment of HypoPT, awareness of concomitant treatment with other drugs is also needed (Table 3).

6.4.6 We advise against routine monitoring of bone mineral density by dual energy X-ray absorptiometry (DXA) scans.

Reasoning:
HypoPT is a state of very low bone turnover and bone mineral density (BMD) is not expected to decrease during the course of HypoPT (90) unless other disorders or drug therapies occur (e.g., glucocorticoids).

6.5. Special circumstances

6.5.1 Autosomal dominant hypocalcaemia (ADH): We recommend frequent monitoring of patients with ADH, who are being treated with calcium and/or activated vitamin D analogues, as such patients may be at high risk of hypercalciuria and renal complications.

Reasoning:
ADH is caused by an activating mutation in the calcium-sensing receptor (CaSR). A diagnosis of ADH can be established through genetic testing (OMIM 601198). The gain of function mutation causes a lowering of the calcium set-point in the parathyroid glands. At equivalent serum calcium levels, patients with ADH have lower PTH levels than normal individuals. In a strict sense, this is not a state of HypoPT, as the parathyroid glands are well preserved although less responsive to a hypocalcemic challenge (91). The CaSR is also expressed in the renal tubule, and renal calcium excretion is often markedly increased in patients with ADH who are at increased risk of renal complications (54;92). In case reports, thiazide diuretics have been reported to reduce urinary calcium in patients with ADH (44;77;93).
6.5.2 Pregnancy and breastfeeding: We suggest treatment with activated vitamin D analogues and calcium supplements as in non-pregnant patients.

Reasoning:

Although pregnancy-related increases in 1,25(OH)₂D initially and in PTHrP later would suggest that calcium and vitamin D analogues may need reducing during pregnancy, this is often not the case. Especially after the 20th week of pregnancy, many women with HypoPT actually need gradually higher doses of activated vitamin D analogues to maintain serum calcium levels in the target range and avoid symptoms of hypocalcaemia (94-96).

There are relatively few case reports and no trials that test management strategies for women with chronic HypoPT during pregnancy and lactation. The largest series included 12 pregnant women who were treated with oral calcium and calcitriol and reported a high level of overall safety during pregnancy (35) (see Appendix 4). These and other authors have recommended oral calcium supplements to be combined with calcitriol (doses of 0.25 to 3.0 ug per day) for treatment of chronic HypoPT during pregnancy (32;35). Other reports support the recommendation to use calcitriol in pregnancy and lactation, due to its potency and short half-life, compared to other forms of vitamin D (94-96), but the amount of evidence is low.

During lactation, PTHrP levels rise and many women develop hypercalcaemia if calcium and activated vitamin D supplements are not often dramatically reduced. Then, gradually after weaning, these changes in maternal hormones regress, and a new steady-state is achieved. Generally, patients with hypoparathyroidism stabilize on a similar if not the same medical regimen as pre-pregnancy, but careful adjustment and monitoring of these patients are needed to assure smooth transition.

6.5.3 We suggest monitoring serum ionized calcium regularly (every 2nd or 3rd week) during pregnancy and breastfeeding with levels to be kept at the lower end of the normal range (serum albumin adjusted total calcium is also acceptable).

Reasoning: Serum total calcium falls in normal pregnancy due to haemodilution-induced reductions in serum albumin levels, but ionized calcium remains stable (34;97). Thus, in pregnant women with HypoPT, serum ionized calcium is the preferred parameter that should be frequently monitored (e.g., every 2 or 3 weeks) (30;32). Alternatively, albumin-corrected total serum is an acceptable parameter to follow (30). Levels of serum calcium are recommended to be kept at the lower end of the normal range in pregnant women with chronic HypoPT. During lactation, there are high rates of bone resorption due to breast tissue production of PTHrP (98). These events mandate careful monitoring of serum calcium levels in women with HypoPT who are nursing because hypercalcaemia is commonly encountered if
vitamin D analogue therapy is not quickly adjusted. The onset of hypercalcaemia during breastfeeding can be immediate (94;98-102) and has even been reported when treating women with HypoPT with longer-acting ergocalciferol, who did not breast-feed (103). Gradually after weaning, the above changes in maternal hormones regress, and a new steady-state is achieved.
Acknowledgement

The authors of the guideline want to thank and acknowledge Kari Lima, MD. Ph.D, Akershus University Hospital, Norway for expert review before sending the Guideline out to ESE Members
Table 1. Symptoms patients should be informed of to allow for early detection of hypo- or hypercalcaemia.

<table>
<thead>
<tr>
<th></th>
<th>Hypocalcaemia</th>
<th>Hypercalcaemia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CNS</strong></td>
<td>Depression</td>
<td>Weakness</td>
</tr>
<tr>
<td></td>
<td>Irritability</td>
<td>Headache</td>
</tr>
<tr>
<td></td>
<td>Confusion or disorientation</td>
<td>Drowsiness</td>
</tr>
<tr>
<td></td>
<td>Seizures</td>
<td>Confusion or disorientation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Poor memory</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reduced concentration</td>
</tr>
<tr>
<td><strong>Neuromuscular</strong></td>
<td>Numbness and tingling (paraesthesia) in circumoral and acral areas (fingers, toes)</td>
<td>Muscle weakness</td>
</tr>
<tr>
<td></td>
<td>Spasms / twitches</td>
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</tr>
<tr>
<td></td>
<td>Cramps</td>
<td></td>
</tr>
<tr>
<td><strong>Cardiovascular</strong></td>
<td>Fast, slow, or uneven heart rate</td>
<td>Fast, slow, or uneven heart rate</td>
</tr>
<tr>
<td></td>
<td>Symptoms of congestive heart failure</td>
<td>Hypertension</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td>Abdominal cramps</td>
<td>Loss of appetite</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nausea / vomiting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Abdominal pain</td>
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<tr>
<td></td>
<td></td>
<td>Constipation</td>
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<tr>
<td><strong>Renal</strong></td>
<td></td>
<td>Polyuria</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dry mouth and or increased thirst</td>
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<tr>
<td><strong>Respiratory</strong></td>
<td>Shortness of breath</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Wheezing</td>
<td></td>
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<tr>
<td></td>
<td>Throat tightness</td>
<td></td>
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</tbody>
</table>
Table 2. Co-morbidities which may occur with an increased prevalence in patients with HypoPT (13;14;22;23;26;27;50;104).

<table>
<thead>
<tr>
<th>Organ system</th>
<th>Co-morbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal</td>
<td>Renal stone disease and impaired renal function</td>
</tr>
<tr>
<td></td>
<td>Renal calcifications</td>
</tr>
<tr>
<td>Immunological</td>
<td>Infections</td>
</tr>
<tr>
<td>Neuropsychiatric</td>
<td>Neuropsychiatric diseases</td>
</tr>
<tr>
<td></td>
<td>Depression</td>
</tr>
<tr>
<td></td>
<td>Impaired quality of life</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Muscle stiffness / pain</td>
</tr>
<tr>
<td></td>
<td>Seizures</td>
</tr>
<tr>
<td></td>
<td>Proximal humerus fractures*</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Ischemic heart disease*</td>
</tr>
<tr>
<td>CNS</td>
<td>Intracerebral calcifications *</td>
</tr>
<tr>
<td>Eyes</td>
<td>Cataract *</td>
</tr>
</tbody>
</table>

* An increased risk has only been documented in nonsurgical HypoPT.
Table 3. Drug therapy and diseases which may interfere with calcium homeostasis and necessitate changes in monitoring and therapy

<table>
<thead>
<tr>
<th>Drug / disease</th>
<th>Mechanism</th>
<th>Possible adverse effects in HypoPT</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loop diuretics</td>
<td>Increased urinary calcium losses</td>
<td>May aggravate hypercalciuria and lower serum calcium levels</td>
<td>Avoid if possible</td>
</tr>
<tr>
<td>Thiazide diuretics</td>
<td>Decreased urinary calcium losses</td>
<td>May increase serum calcium levels</td>
<td>May be used in a patient with HypoPT (see text, section 3.7)</td>
</tr>
<tr>
<td>Systemic glucocorticoids</td>
<td>Decreased intestinal calcium absorption and increased urinary calcium losses</td>
<td>May cause hypocalcaemia</td>
<td>Avoid if possible</td>
</tr>
<tr>
<td>Antiresorptive drugs</td>
<td>Decreased bone turnover</td>
<td>May cause hypocalcaemia</td>
<td>Rarely needed, as HypoPT is a state of (very) low bone turnover</td>
</tr>
<tr>
<td>Proton pump inhibitors (PPI)</td>
<td>May cause hypomagnesaemia</td>
<td>May lower serum calcium levels and cause symptoms similar to hypocalcaemia</td>
<td>Avoid if possible – otherwise magnesium supplements as needed</td>
</tr>
<tr>
<td>Chemotherapy: Cisplatin, 5-Fluorouracil, Leucovorin</td>
<td>May cause hypomagnesaemia</td>
<td>May lower serum calcium levels and cause symptoms similar to hypocalcaemia</td>
<td>Magnesium supplements, as needed</td>
</tr>
<tr>
<td>Cardiac glycosides (e.g., digoxin)</td>
<td>Hypercalcaemia may predispose to digoxin toxicity</td>
<td>Hypocalcaemia may reduce the efficacy of digoxin</td>
<td>Arrhythmias</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Avoid if possible. If needed, close monitoring by a cardiologist</td>
</tr>
<tr>
<td>Diarrhea / gastrointestinal disease</td>
<td>May reduce intestinal absorption of calcium and vitamin D</td>
<td>May cause hypocalcaemia</td>
<td>Close monitoring of serum calcium levels with dose adjustments as needed</td>
</tr>
<tr>
<td>Changes in (correction of) acid-base balance*</td>
<td>The affinity of calcium to bind to proteins in serum is highly pH dependent – only the free fraction in physiological active</td>
<td>Correction of metabolic acidosis may cause hypocalcaemia</td>
<td></td>
</tr>
<tr>
<td></td>
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<td></td>
</tr>
<tr>
<td>Immobilization</td>
<td>Increased bone resorption. In healthy individuals, PTH and 1,25-dihydroxyvitamin D levels are suppressed.</td>
<td>May cause hypercalcaemia</td>
<td></td>
</tr>
</tbody>
</table>

* Changes in the free (ionized) fraction of serum calcium (Ca\(^{2+}\)) cannot be monitored by measuring total calcium levels. Many laboratories report serum Ca\(^{2+}\) levels adjusted to a neutral pH value (pH 7.4), which does not reflect the actual serum Ca\(^{2+}\) level in a patient with disturbances in acid-base balance. If so, patients may have symptoms despite (apparently) normal calcium levels and Ca\(^{2+}\) levels at actual pH should be requested.
Figure 1

Monitoring and Treatment of Chronic Hypoparathyroidism in Adults

Re-evaluation
Every 3-6 months
- S-Ca
- S-PHos
- S-Alk Phos
- eGFR (once a year: 24 h U-Ca, S-25OHDL)

Primary targets reached?
- Serum Ca\(_{\text{crit}}\): 2.10-2.35 mmol/L
- No symptoms of hypocalcemia

Consider optimization of secondary targets:
- if achlorhydria or use of PPI consider calcium citrate (#6.3.5)
- if hypercalciuria reduce calcium intake, sodium-restricted diet and/or thiazide diuretic (#6.5.7)
- if hyperphosphatemia: phosphate-lowering diet, decreased dose of activated vitamin D with increased dose of calcium supplements (#6.3.5)
- if decline in renal function (↓ eGFR): renal imaging (Stones or Calcineurin?)
- if hypomagnesemia: add magnesium supplements
- if S-25OHDL < 75 nmol/L: add vitamin D supplements

Optimize treatment
- Adjust dose of calcium and/or activated vitamin D
- if hypomagnesemia: add magnesium supplements
- if S-25OHDL < 75 nmol/L: add vitamin D supplements

a) If dose of calcium or activated vitamin D is changed: Re-evaluation of serum calcium levels is recommended weekly or twice a week.


49. Cusano NE, Rubin MR, McMahon DJ et al. PTH(1-84) is associated with improved quality of life in hypoparathyroidism through 5 years of therapy. J Clin Endocrinol Metab 2014; 99(10):3694-3699.


33


