# Insight

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## Global Expert Summit on Hypoparathyroidism: Intervening to decrease long term complications 2-3 December 2021

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European Society of Endocrinology

# Welcome to this summary of the virtual Global Expert Summit on Hypoparathyroidism (GESH), which took place on 2–3 December 2021.

## The theme of GESH 2021 was 'Intervening to decrease long term complications'.

The Summit's objectives were:

• to understand how impaired mineral homeostasis in patients with chronic hypoparathyroidism may create a cascade of changes across organ systems, leading to adverse clinical outcomes, and how these long term outcomes might be improved

• to summarise specific considerations for special patient populations with chronic hypoparathyroidism and specific complicated clinical situations, such as the COVID-19 pandemic, and also pregnancy

• to review results for achievement of mineral homeostasis and organ protection.

With a balance between presentations and interactive panel discussions, the Summit provided an excellent forum for high level scientific discussion. This report serves to extend the valuable educational experience provided by the Summit to the broader international community.

***GESH 2021 Organising Team***


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Takeda

Takeda initiated, organised and funded the **Global Expert Summit on Hypoparathyroidism: Intervening to decrease long term complications**, which was held online on 2–3 December 2021, to benefit healthcare providers from around the world.

The highlights of this summit reflect the scientific opinions and experiences of the individual presenters and may not necessarily reflect the opinions of Takeda, or any of its subsidiaries, partners or employees.

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# Event highlights

SESSION 1

## Understanding and improving outcomes

Chronic hypoparathyroidism (hypoPT) is a rare endocrine disease. Post-surgical hypoPT is most common, and considered permanent if it persists beyond 12 months. Non-surgical hypoPT can have many causes and is often misdiagnosed. Diagnostic factors include hypocalcaemia, parathyroid hormone (PTH) deficiency, elevated serum phosphorous, reduced vitamin D, and elevated urinary calcium. Complications may include cataracts, infection, renal impairment, cardiovascular events and skeletal abnormalities.

The risk of renal failure in patients with post-surgical hypoPT is about three times higher than in the general population. Renal function is affected by multiple hormones and PTH may have a regulatory effect. Administration of recombinant human PTH (rhPTH(1–84)) has been shown to preserve glomerular filtration rate. Patients with hypoPT have also been shown to be at greater risk of cardiovascular disease and vascular calcifications compared with the general population.

In the skeleton, hypoPT can cause decreased bone turnover, increased density and altered microstructure. Around a third of patients with post-surgical hypoPT may have osteopenia. While there appears to be a skeletal phenotype of hypoPT, it is not clear whether there are significant clinical consequences. Overall fracture risk does not seem to be affected.

Quality of life (QoL) is impaired in patients with hypoPT. Generic instruments for assessing QoL have limitations, and disease-specific tools may enable more reliable evaluation. The Hypoparathyroidism Patient Questionnaire (HPQ) is a patient-based 28-item instrument which has been shown to identify correlations between QoL, biochemical parameters and different types of treatment. It is easy to implement in clinical practice and can be used annually or during treatment changes.

Currently, we do not have a clear definition of adequate control in hypoPT. Delphi exercises that looked at biochemistry and patient evaluation found that around a third of patients may be inadequately controlled. This may include poor biochemical control, hypercalciuria, hyperphosphataemia, gastrointestinal issues and reduced QoL. Some patients may have poor biochemical control but feel well, while others may be symptomatic with satisfactory biochemical results, which makes treatment challenging. Prospective data will help improve the definition of adequate control.

SESSION 2

## Management in special groups and circumstances

Patients with chronic hypoPT are at increased risk of infection and around two to three times more likely to be admitted to hospital than healthy controls. Predictors for infection include elevated phosphate, a higher number of hypercalcaemic episodes and longer duration of disease. The risk may be associated with deficiencies in calcium and PTH. Case reports suggest that COVID-19 infection can unmask, cause and worsen hypoPT. There has been some vaccine hesitancy among patients with hypoPT, but vaccination should be encouraged, as the risks associated with COVID-19 infection are much higher.

There are limited data on pregnancy outcomes in women with chronic hypoPT. A registry study in Sweden found that most patients with hypoPT have normal pregnancy outcomes, though there is an increased risk of induction and of lower infant birth weights. Therapy should focus on avoiding hypocalcaemia and hypercalcaemia, and serum calcium should be monitored regularly. Pooled data from Canada and Denmark indicated that around a fifth of pregnant patients with hypoPT require significant adjustment of active vitamin D and calcium doses. Two case reports showed that PTH therapy had no ill-effects on the fetus, but this is not currently recommended as there are insufficient safety data.

SESSION 3

## Moving beyond conventional therapy

Conventional therapy for hypoPT involves supplementation with oral calcium and vitamin D. It does not replace the lack of PTH and can have long term adverse effects, such as renal impairment. In contrast, PTH treatment reduces the need for calcium and vitamin D supplementation, restores phosphate homeostasis, and seems to preserve renal function. PTH has been shown to be better tolerated than conventional therapy in patients with hypoPT who have kidney disease. PTH therapy may also lower cardiovascular disease risk in chronic hypoPT, though further studies are needed.

Conventional therapy does not address the skeletal abnormalities characteristic of hypoPT. There is growing evidence that PTH therapy may ameliorate bone metabolism and structure. Several studies have shown improvements in bone turnover and bone mass density in patients taking rhPTH(1–84).

Multiple preparations of PTH are in development, though subcutaneous rhPTH(1–84) is the only one currently available for hypoPT. Orally administered TransCon PTH(1–34) may allow more stable release of PTH into the circulation, and has been shown to decrease dependence on vitamin D and calcium supplementation and improve biochemical control.

The Second International Workshop on Parathyroid Disorders has prepared new guidance for the diagnosis and management of hypoPT, which will be published in *Journal of Bone & Medical Research* in 2022. The new guideline confirms the need to pursue PTH therapy.

# Keynote: **Diagnosing hypoparathyroidism – what matters**

**Maria Luisa Brandi** *(Italy)*

Chronic hypoparathyroidism (hypoPT) is a rare endocrine disease, but still affects a great number of people across the world. Data on prevalence are limited and recent estimates are hugely varied, due to differences in defining the condition. For example, prevalence in Norway is estimated to be 10.2 per 100 000 people,[1] compared with 24 per 100 000 in Denmark.[2] Prevalence appears to be higher in the USA. Post-surgical hypoPT is the most common form of the disease, with one survey finding that 67.6% of cases arose from post-surgical complications.[3] Idiopathic hypoPT accounted for 14.6% of cases.

**Misdiagnosis of idiopathic hypoPT**

Understanding best practice for the diagnosis of chronic hypoPT is important, because it is often misdiagnosed. Results from a large-scale study carried out in China indicated that, between 2009 and 2013, 26.7% of 430 patients with idiopathic hypoPT were misdiagnosed.[4]

The mean delay in receiving an accurate diagnosis of idiopathic hypoPT is nearly 6 years from the first onset of symptoms, and some patients are inappropriately treated for epilepsy.[5] Most patients with post-surgical hypoPT are diagnosed immediately, while non-surgical hypoPT tends to take longer to diagnose.

**Patient presentation and complications**

The aetiology of hypoPT is varied. As noted, post-surgical hypoPT is most common, but causes can also include autoimmune dysfunction, genetics, mineral deposition, radiation, maternal hypoPT and other factors.

Common symptoms include hypocalcaemia, paraesthesia around the fingers, toes and mouth, and neuromuscular irritability. There may also be symptoms related to the central nervous and cardiovascular systems.

Complications may include cataracts, infection, kidney stones, renal dysfunction, depression, seizures and cardiovascular events.

**Diagnostic criteria**

The diagnostic criteria for chronic hypoPT are straightforward. According to the new consensus on management of hypoPT (further discussed by Aliya Khan on page 18), a diagnosis should be made where there is evidence of:

- hypocalcaemia (low ionised serum calcium or total serum calcium adjusted for albumin) in the presence of an undetectable or inappropriately low level of intact parathyroid hormone (PTH) (utilising either a second or third generation assay) on two occasions, at least 2 weeks apart
- additional abnormalities that support a diagnosis of chronic hypoPT, including elevated serum phosphorous, reduced vitamin D, or an elevated urinary fractional excretion of calcium
- post-surgical hypoPT, where the condition is regarded as permanent if it persists for more than 12 months after surgery.

An important aspect of the evaluation of patients who have undergone thyroid surgery is predicting whether the transient hypoPT which is often observed in these individuals will become permanent.

A recent systematic review found that if PTH values exceed 10pg/ml (1.05pmol/l) at 12–24 hours after surgery, then permanent chronic hypoPT is unlikely, provided that any long term need for active vitamin D or calcium supplementation is addressed. Therefore, the new guidance recommends measuring PTH immediately after total thyroidectomy to rule out hypoPT. PTH levels below 10pg/ml (1.05pmol/l) at 12–24 hours post-surgery have less predictive value, and development of hypoPT remains a possibility.

**Genetic and autoimmune diagnoses**

Additional analyses of the literature support the development of a clinical approach to the genetic aetiology of hypoPT. Currently there is no routine assay for assessment of autoimmune-related hypoPT. The group that developed the new guidelines reviewed current genetic testing capabilities, including single gene tests, disease-targeted gene panels, exome and genome sequencing, and various tests for the detection of chromosomal abnormalities.

Where a genetic cause of hypoPT is suspected, the group's recommendations are as follows.

- Genetic testing should be offered to patients with hypoPT who have a positive family history of non-surgical hypoPT, together with syndromic features, or who are under 40 years old.
- Genetic testing for autoimmune regulator variants should be undertaken in patients with non-surgical hypoPT who have other clinical features of autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED).
- The designation of autoimmune hypoPT should be avoided in patients who do not have APECED, because there is currently no definitive diagnostic test for polygenic autoimmune hypoPT.

**Knowledge gaps**

Further research should investigate the use of antibodies in the diagnosis of hypoPT. Validated assays are also needed, particularly for the calcium-sensing receptor, which may be linked with immune checkpoint inhibitor treatment-associated disease. More research is needed to determine the best genetic testing modalities, and to test the utility of early predictors of permanent post-surgical hypoPT.

## Key learning points

- **HypoPT is rare and often misdiagnosed**
- **Post-surgical hypoPT is most common and regarded as permanent if it persists beyond 12 months**
- **Measuring PTH immediately after total thyroidectomy can rule out hypoPT**
- **New diagnostic guidelines set out specific parameters for hypocalcaemia, elevated serum phosphorous, reduced vitamin D, elevated urinary calcium, and use of genetic testing**

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# Session 1: **Understanding and improving long term outcomes in patients with chronic hypoparathyroidism**

## Is renal dysfunction linked to hormonal imbalance in hypoparathyroidism?

**Andrea Giustina** *(Italy)*

Hypoparathyroidism (hypoPT) is characterised by low levels of endogenous parathyroid hormone (PTH), often caused by the removal of the parathyroid glands during thyroidectomy. HypoPT can cause kidney disease, and the risk of renal failure in patients with post-surgical hypoPT is about three times higher than in the general population.[1]

**Renal dysfunction in patients with hypoPT**

Conventional therapy for hypoPT corrects hypocalcaemia by increasing intestinal calcium absorption, but does not mediate renal calcium reabsorption or urinary phosphate excretion. Elevated urinary calcium is associated with an increased risk of nephrocalcinosis, nephrolithiasis and chronic kidney disease (CKD).[2]

Hormonal abnormalities such as those involving fibroblast growth factor-23, klotho, the renin-angiotensin-aldosterone system, vasopressin, and the growth hormone–insulin-like growth factor-1 axis may also contribute to renal complications in patients with hypoPT, often because of PTH action.

**ENDORSE study**

The Endocrine Determinants of Renal Function in Patients with HypoPT (ENDORSE) Study is a cross-sectional observational study performed to test the hypothesis that hypoPT causes abnormalities in renal function that predispose patients to develop renal insufficiency. Analysis will identify any differences in the hormonal axes between patients who have disease that is well or not well controlled by conventional treatment.

The interim analysis shows a high prevalence of CKD (61.5%) in patients with hypoPT. It supports the hypothesis that other PTH-related hormonal mechanisms might also contribute to impaired renal function in patients with hypoPT, advocating towards the use of PTH in treatment of hypoPT.

The results also point to renin levels as a potential new prognostic marker and target for disease control.

### Key learning points

- **HypoPT increases the risk of renal impairment**
- **Renal function is affected by multiple hormones which can be influenced by PTH**
- **The use of PTH in treatment of hypoPT may offer better renal protection than conventional treatment**

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## Renal calcification in patients with chronic hypoparathyroidism

**Claudio Marcocci** *(Italy)*

Patients with chronic hypoparathyroidism (hypoPT) are at increased risk of impaired mineral homeostasis and renal complications compared with the general population. Treatment with conventional therapy, consisting of oral administration of calcium and activated vitamin D, is suboptimal and does not replace the lack of parathyroid hormone.

A 2018 study of 90 patients with chronic hypoPT found that only 34% met all four targets set out in the 2015 European Society of Endocrinology guidelines for management of post-operative chronic hypoPT (albumin-adjusted serum calcium, serum phosphate, calcium–phosphate product and 24-hour urinary calcium).[1] These results are consistent with other studies that have shown an increased risk of renal complications in chronic hypoPT. Multiple studies have also demonstrated that renal calcification is common in these patients, though results are variable.

A similarly sized 2021 case-control study investigated the rate of renal calcification and its relationship with quality of life (QoL) in post-surgical chronic hypoPT. Results showed that 29.2% of patients had renal calcifications demonstrated by ultrasound.[2] In addition, 48.3% of patients reported symptoms of hypocalcaemia. Renal calcifications were not correlated with 24-hour urinary calcium excretion and there was no difference in estimated glomerular filtration rates between those with chronic hypoPT and controls. Patients with renal calcifications and/or symptoms of hypocalcaemia had a statistically significantly lower QoL, compared with those without symptoms. Adequate biochemical control was achieved in only a third of patients treated with conventional therapy.

**Implications for patient management**

These findings indicate that conventional therapy in post-surgical chronic hypoPT is suboptimal. Patients have symptoms of hypocalcaemia, renal calcification and decreased QoL.

This underscores the importance of careful monitoring of patients with chronic hypoPT who are receiving conventional treatment. Such monitoring might include measurement of 24-hour urinary calcium excretion and renal imaging.

### Key learning points

- **Patients with post-surgical chronic hypoPT are at increased risk of renal impairment**
- **Conventional therapy in post-surgical chronic hypoPT is suboptimal, and patients have renal calcifications and decreased QoL**
- **Monitoring patients with chronic hypoPT is essential**

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# Long term effects of hypoparathyroidism on renal function

**Markus Ketteler** *(Germany)*

Chronic kidney disease (CKD) is a common condition. Small, early changes in renal function, as measured by estimated glomerular filtration rate (GFR), can have a large impact on risk profile. Significant symptoms of CKD start to appear with a GFR of <60ml/min.

**Role of PTH in renal physiology**
Parathyroid hormone (PTH) increases calcium reabsorption, induces magnesium reabsorption and inhibits phosphate reabsorption. Both PTH deficiency and high doses of vitamin D (as associated with conventional treatment for chronic hypoparathyroidism (hypoPT)) can create a urine environment prone to calcium precipitation. Patients with chronic hypoPT are at increased risk of nephrolithiasis and CKD.[1]

**Renal consequences of chronic hypoPT**
A 2021 retrospective cohort study compared the risk of renal complications and decline in renal function in more than 8000 patients with chronic hypoPT and 40 000 control subjects.[2] Patients with chronic hypoPT were nearly seven times more likely to develop nephrocalcinosis and twice as likely to develop nephrolithiasis than controls. They also had an increased risk of CKD and a decline in estimated GFR of 30% or more from baseline.

**Limiting GFR decline with PTH replacement**
Data on PTH replacement are limited, as cohorts are small. A 5-year controlled clinical trial found that administration of recombinant human PTH(1–84) (rhPTH(1–84)) resulted in a very stable estimated GFR over the follow-up period.[3] A 2020 retrospective study confirmed that estimated GFR was preserved among patients who received rhPTH(1–84) treatment and declined in those who did not.[4]

**Parathyroidectomy and kidney transplantation**
Parathyroidectomy in kidney transplant recipients with chronic hypoPT can impair graft survival by 60%.[5] Therefore, clinical practice guidelines recommend that patients who need both surgeries should undergo parathyroidectomy before transplantation.

## Key learning points

- **Physicians managing patients with chronic hypoPT should be aware of the high risk of renal dysfunction**
- **PTH deficiency is associated with an increased risk of kidney impairment and CKD, which may be exacerbated by treatment with active vitamin D**
- **PTH replacement therapy results in a stable estimated GFR**

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# Renal and cardiac disease in patients with hypoparathyroidism

**Lars Rejnmark** *(Denmark)*

Chronic hypoparathyroidism (hypoPT) can lead to renal complications including hypercalciuria, hyperphosphataemia (reduced renal excretion of phosphorus), renal calcifications and impaired renal function.[1] We normally aim to lower calcium levels in patients with chronic hypoPT to avoid hypercalciuria.

Hypercalciuria is associated with increased risk of renal stones. Its prevalence in patients with chronic hypoPT ranges from 38% in the USA to 56–66% in Denmark, compared with around 5–10% in the general population. The estimated prevalence of renal calcifications in patients with chronic hypoPT ranges from 1.9% to 43%. This variation may be explained by differences in study methodology.

**Renal insufficiency in chronic hypoPT**
Patients with chronic hypoPT are at increased risk of chronic kidney disease.[2] Hypercalciuria and renal calcifications do not fully explain the renal insufficiency in chronic hypoPT, but biochemistry does matter. A case-control study demonstrated that an elevated calcium–phosphate product, a higher number of hypercalcaemic episodes and longer duration of chronic hypoPT are all significantly related to elevated risk of any renal disease.[3]

**Role of PTH in renal insufficiency**
Parathyroid hormone (PTH) deficiency in patients with chronic hypoPT may contribute to renal impairment. PTH and PTH-related protein could be potent modulators of renal haemodynamics and glomerular filtration rate (GFR).

This is supported by the observation that kidney function is affected by parathyroidectomy in primary hyperparathyroidism. Lowering PTH levels in patients with this condition has been shown to sustain a reduction in estimated GFR.[4]

Patients with hypoPT have also been shown to be at greater risk of cardio- and cerebrovascular disease compared with the general population.[2] Risk of renovascular diseases is increased in chronic hypoPT. Further studies should consider whether this is due to disturbances in mineral homeostasis, PTH deficiency, or both.

## Key learning points

- **Patients with chronic hypoPT are at increased risk of renal impairment and vascular disease**
- **Lowering calcium levels helps to avoid hypercalciuria**
- **PTH deficiency may contribute to renal insufficiency**

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# Hypoparathyroidism: altered mineral handling, bone structure and fracture risk

**John P Bilezikian** *(USA)*

The skeleton is a disease target in patients with chronic hypoparathyroidism (hypoPT). Abnormal mineral handling is associated with altered bone quality and increased fracture risk.[1]

**Skeletal features affected by hypoPT**

In the skeleton, chronic hypoPT can cause decreased bone turnover, increased density and altered microstructure. Trabecular bone volume, thickness and connectivity may be increased. The bone remodelling cycle has been shown to be prolonged by 55 days in patients with chronic hypoPT, with bone formation decreased by 80%.[2]

Changes in bone turnover can be measured using bone turnover markers, histomorphology and tetracycline labelling. Clinical decision making is usually based on bone biopsy.

**Structural features of bone in chronic hypoPT**

The most clinically relevant measurement is bone density by dual-energy X-ray absorptiometry. This has been used to demonstrate a positive correlation between bone density and duration of hypoPT.[3]

In chronic hypoPT, trabecular bone takes on the appearance of cortical bone. A study of 82 patients with post-surgical chronic hypoPT showed that 32.4% had osteopenia.[4] These changes in bone structure do not appear to be associated with an increase in bone strength.

**Fracture risk in hypoPT**

Fracture risk assessment can be puzzling. Since bone mineral density is high in chronic hypoPT, fracture incidence should be reduced. However, since reduced bone turnover leads to hypermature bones, fracture incidence may increase.

Overall fracture risk in patients with chronic hypoPT is not significantly different from that in healthy subjects. Patients with post-surgical disease appear to have a lower risk of upper extremity fractures than non-surgical patients.[5] A 2021 systematic review and meta-analysis indicated a significantly increased risk of vertebral fractures in post-surgical patients.[6]

Normalising skeletal metabolism in patients with chronic hypoPT is desirable, though the potential clinical consequences remain unclear.

## Key learning points

- **Available data indicate that lack of PTH alters skeletal dynamics, bone density and microstructure**
- **These skeletal changes may or may not be associated with clinical consequences, such as risk of fractures**

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# Disease-specific assessments for quality of life in chronic hypoparathyroidism

**Heide Siggelkow** *(Germany)*

Quality of Life (QoL) is the degree to which an individual is healthy, comfortable and able to enjoy life events. Standard indicators include wealth and employment, environment, physical and mental health, education, recreation and social belonging.

QoL is impaired in patients with chronic hypoparathyroidism (hypoPT). The inverse relationship between self-reported symptom severity and decreased QoL has been demonstrated with generic instruments such as the 36-item Short Form Survey (SF-36 v2.0) and the EuroQoL 5 Dimensions (EQ-5D-5L).[1]

**Effective evaluation of QoL in patients with hypoPT**

The limitations of generic instruments when assessing QoL have prompted the development of multiple disease-specific instruments, including the Hypoparathyroidism Patient Diary,[2] the Hypoparathyroidism Patient Experience Scale-Symptom,[3] the Hypoparathyroidism Patient Experience Scale-Impact[4] and the Hypoparathyroidism Patient Questionnaire (HPQ), a 28-item instrument developed using a patient-based analytical–empirical approach.[5]

The HPQ has been used to differentiate specific symptoms in patients with different disease aetiology, and to investigate the wide range of parameters that influence QoL in patients with chronic hypoPT. For example, calcium–phosphate product was found to be the biochemical parameter most closely correlated with symptom severity.[5]

**Generic versus disease-specific instruments**

Generic and disease-specific instruments for QoL yield different results when evaluating the effects of treating chronic hypoPT with recombinant human parathyroid hormone (1–84) (rhPTH(1–84)). Studies using SF-36 found no significant effect of rhPTH(1–84) treatment on QoL. However, an evaluation of 15 patients treated with rhPTH(1–84) found significant improvements using HPQ-28 over eight evaluations.

To date, results obtained through disease-specific questionnaires suggest no effect on QoL of underlying thyroid disease or disease duration, but biochemical parameters, disease aetiology, age and gender all have an effect.

## Key learning points

- **Generic instruments for measuring QoL have limitations**
- **Several disease-specific instruments have been developed to assess QoL in patients with chronic hypoPT**
- **These instruments reliably detect QoL changes associated with effective treatment and permit analysis of the correlation between QoL, biochemical parameters and treatment**

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# Panel discussion: **Protecting organs from progressive damage in chronic hypoparathyroidism**

*Expert panel:* **John P Bilezikian** *(Chair, USA)*, **Maria Luisa Brandi** *(Italy)*, **Andrea Giustina** *(Italy)*, **Elvira O Gosmanova** *(USA)*, **Markus Ketteler** *(Germany)*, **Claudio Marcocci** *(Italy)*, **Lars Rejnmark** *(Denmark)*, **Heide Siggelkow** *(Germany)*

**The panel of experts gave their personal insights on the long term effects of hypoparathyroidism (hypoPT) and strategies for protecting organs from progressive damage.**

**Giustina:** Findings on the hormonal factors that may be relevant to renal pathophysiology in patients with hypoPT are preliminary. The presence of hypocalcaemia and renal dysfunction seems to be quite strictly related to low renin. It is difficult to draw definitive conclusions about whether this is related to low parathyroid hormone (PTH) or is a specific function of hypocalcaemia.

**Gosmanova:** 'The jury is still out' regarding the importance of measuring 24-hour urinary calcium excretion. It shows significant day-to-day variability, so a single 24-hour urine collection may not reflect chronic urinary calcium excretion or steady state calcium status. Based on urinary calcium levels in the general population, we may also be using much higher cut-offs to define hypercalcemia than we should.

**Ketteler:** Nephrology research has mostly focused on secondary hyperparathyroidism and its influence on vascular calcifications and on hypertension. The effects of hypoPT on renal haemodynamics and renal outcomes have not been systematically studied. Now that it is possible to replace PTH, there is an opportunity to investigate this. The effect of microcalcifications, which are not seen in conventional ultrasounds, is also an area for future research.

**Marcocci:** The relationship between hypercalciuria and nephrocalcinosis is now confirmed. More studies are needed to better understand the relationship between urinary calcium excretion and renal function in patients with chronic hypoPT. We started an animal model a few months ago, to study the effects of parathyroidectomy, which may provide data on wider renal outcomes.

**Gosmanova:** Chronic kidney disease contributes to an array of adverse outcomes, including cardiovascular effects. Therefore, maintenance of normal function is of the utmost significance. Patients treated in observational studies with recombinant PTH seem to maintain stable renal function when compared with historical controls. Why we see that observation is still not fully established, but we know patients who receive PTH replacement require significantly lower doses of oral calcium and active vitamin D. Conventional therapy cannot restore normal homeostasis. Using recombinant PTH gives us an opportunity to address physiological deficits in hypoPT, maintain calcium levels and restore phosphate homeostasis.

**Giustina:** Given the vasoactive properties of PTH, hypertension may be an important factor. It is better to understand hormonal imbalance and have a clear physiological picture before using anti-hypertensive or angiotensin-converting enzyme inhibitor drugs in patients with hypoPT.

**Brandi:** Measuring calcium could help to reduce the delay in diagnosing hypoPT in non-surgical patients. Many thyroid disorders are not recognised early because they are referred to psychiatry or neurology. Where post-surgical patients are hypocalcaemic but not reaching the threshold for likely permanent hypoPT, one solution is to avoid using very high doses of activated vitamin D after surgery, which can act detrimentally on the function of the parathyroid tissue. We want to encourage the parathyroid tissue to work post-surgery to prevent permanent dysfunction. Another possibility is to use calcium supplements and teriparatide instead of high doses of calcitriol.

**Bilezikian:** The increase in fracture risk observed in patients with non-surgical hypoPT is most likely due to duration of disease.

**Rejnmark:** Patients with non-surgical hypoPT will have been suffering from the disease much longer than those with post-surgical hypoPT. Those with non-surgical hypoPT are also a very heterogeneous group: some of the many different reasons for developing non-surgical hypoPT may, by themselves, affect bone metabolism and fracture risk.

**Bilezikian:** From a therapeutic point of view, it is desirable to normalise skeletal metabolism. However, there is some debate about whether skeletal metabolism is worth addressing if there are no adverse clinical consequences. This is abnormal bone by several measures, yet patients don't seem to be badly affected. PTH may optimise management of hypoPT, and a secondary benefit may be to normalise skeletal metabolism and microstructure.

**Rejnmark:** There is a reason that bones are remodelled throughout our lives. If patients are suffering from hypoPT, this remodelling is markedly reduced. I do think it is very important to try to normalise bone remodelling in these patients.

**Brandi:** We are analysing the number of fractures, but not how they are healing. Observing fracture healing might be an important observation.

**Siggelkow:** The disease-specific questionnaire (HPQ-28) is easy to use in clinical practice. It can be used during treatment changes or once or twice a year to document symptoms and complaints. It is freely available and just needs to be translated for specific countries.

## Key learning points

- **There are many new opportunities to investigate the relationship between hypoPT and specific parameters of renal function, particularly in the context of PTH replacement therapy**
- **Chronic hypoPT is associated with long term skeletal changes, and it seems desirable to address these, even in the apparent absence of significant clinical consequences**
- **Disease-specific questionnaires can help assess the long term impact of hypoPT symptoms on quality of life**

# Adequate control in hypoparathyroidism: a definition and case study

**Neil Gittoes** *(UK)*

There are significant gaps in our knowledge of chronic hypoparathyroidism (hypoPT). These include the long term consequences of the disorder, what constitutes optimal care and adequate disease control, and whether replacement of parathyroid hormone (PTH) can decrease morbidity.[1]

Understanding how short term biochemical results relate to long term outcomes will help us find ways to improve management beyond conventional treatment. More innovative therapies such as replacement PTH may mitigate against some of the long term effects of chronic hypoPT, particularly renal and bone outcomes.

The aetiology and effects of chronic hypoPT vary by patient, but adverse consequences can extend to virtually all organ systems.

**Issues in defining (in)adequate control**

Current guidelines are based primarily on short term patient follow-up data. A question remains about what constitutes adequate or inadequate control over disease. More research is needed to understand if short term biochemical parameters equate to long term positive outcomes. The Physicians Advancing Disease Knowledge in Hypoparathyroidism (PARADIGHM) Study, a long term natural history registry of patients with chronic hypoPT, should answer some of these questions.

Generally, the more abnormal the biochemical results and the more severe the symptoms and impact on quality of life (QoL), the more likely it is that the condition is not adequately controlled.

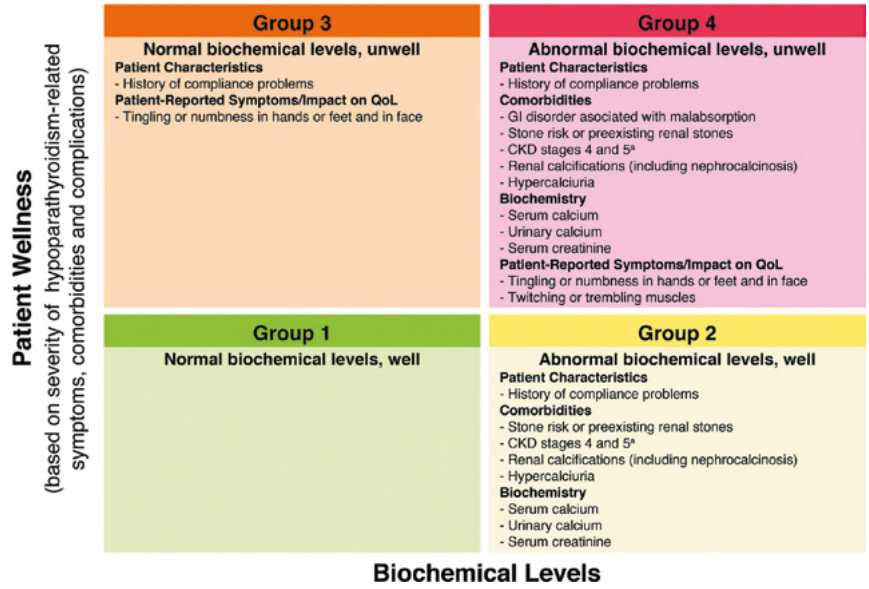
Characteristics of patients not adequately controlled on standard therapy include poor control of serum calcium concentration, high levels of calcium and vitamin D needed to control symptoms, hypercalciuria and other renal issues, hyperphosphataemia, gastrointestinal issues impeding calcium and vitamin D absorption, and reduced QoL.

**Consensus on inadequate control through Delphi**

A Delphi process has been applied to attempt to combine biochemistry and broader patient evaluation in a definition of inadequately controlled chronic hypoPT. A consensus among experts from Portugal, Sweden and the UK found that around a third of patients may be inadequately controlled.[2] The figure below shows characteristics of well-controlled patients (group 1, 63%) and three sub-categories of patients who are not adequately controlled (group 2, 13%; group 3, 12%; group 4, 9%; these percentages are estimates made by Delphi panellists).

If we translate these sub-categories of inadequately controlled disease to cases, patients may experience one of several scenarios:

- persistent poor biochemical control with symptoms of hypocalcaemia, the treatment of which may cause episodes of hypercalcaemia requiring emergency care
- persistent hypercalciuria, symptomatic stone disease and declining renal function despite conventional treatment
- multiple neurocognitive symptoms negatively impacting QoL, with acceptable routine biochemistry
- symptomatically 'well', but with chaotic biochemical control (perhaps of greater concern to the clinician than the patient).




Characteristics that achieved consensus as 'very important' or 'important' among Delphi panellists in Portugal, Sweden and the UK for groups 2–4 of patients with chronic hypoPT whose disease is not adequately controlled on conventional therapy. CKD, chronic kidney disease; GFR, glomerular filtration rate; GI, gastrointestinal; QoL quality of life. [a]Defined as GFR<30ml/min/1.73m$^2$ on dialysis.


**Impact of inadequate control on health services**

An analysis of data extracted from the Hospital Episode Statistics data repository in England indicated that the prevalence of co-morbidities was consistently higher in patients in the non-surgical hypoPT sub-cohort compared with the post-surgical hypoPT group, regardless of the number of co-morbidities.[3]

Those with hypoPT were also at significantly increased risk of neuropsychiatric conditions, renal insufficiency, infections, infarction and nephrolithiasis, compared with those who underwent thyroid surgery without development of hypoPT. Renal co-morbidities were more than eight times higher in patients with post-surgical hypoPT. In 0.02% of patients, healthcare costs exceeding £60 000 were accrued, driven by renal complications.

Patients with inadequately controlled chronic hypoPT also have high symptom severity which is correlated with impaired QoL.[4]

More data are needed on long term biochemical outcomes and patient well-being, for different types of treatment.[5]

## Key learning points

- **Adequate control in patients with chronic hypoPT can be defined based on short and long term goals, and according to biochemical and clinical parameters**
- **Patients with chronic hypoPT are likely to have significant co-morbidities, particularly due to renal complications**
- **Registries such as PARADIGHM will provide much-needed data on long term outcomes in patients managed with conventional therapy or recombinant human PTH**

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# Panel discussion: **How effective are we in achieving adequate control in our patients?**

*Expert panel:* **Bart L Clarke** *(USA, Moderator)*, **John P Bilezikian** *(USA)*, **Neil Gittoes** *(UK)*, **Andrea Giustina** *(Italy)*

**The expert panel discussed issues surrounding the achievement of adequate control in patients with hypoparathyroidism (hypoPT).**

**Gittoes:** We do not have a clear definition of adequate control, which makes it a moving target. Lack of awareness of hypoPT among patients and clinicians results in suboptimal management and unmet need. International guidelines will help to pull the evidence base together, promote awareness and empower patients to demand better care.

**Bilezikian:** The average endocrinologist in the USA has a census of only one or two patients with hypoPT, therefore education is very important.

**Giustina:** We need to raise awareness of hypoPT as a potentially severe disease. Many doctors see hypoPT simply as an issue of calcium balance. Adding clinical parameters to the evaluation of inadequate disease control would help to attract appropriate clinical attention.

**Gittoes:** Data relating to adequate and inadequate control over mineral homeostasis and the link with bone parameters and healthcare resource utilisation have been limited.

**Bilezikian:** Unlike conventional therapy, recombinant parathyroid hormone (PTH) therapy can make a big difference in bone metabolism, remodelling and microstructure. Whether that translates into a clinical outcome is another question. Some are not even convinced that this matters, so there is a need for more data.

**Clarke:** More prospective data are needed. We have biochemical knowledge, but the outcomes of interventions are unclear. Compared with other endocrine diseases, hypoPT is under-served. To move the field forwards, prospective databases could possibly prioritise biochemical evaluation. Given the absence of clinical consequences, the effect on bone is perhaps not a near term priority to guide interventions that could improve quality of life (QoL). We cannot look at everything.

**Gittoes:** Hypothyroidism is a good comparative case for hypoPT studies. There is a perception that hypoPT is a minor issue that can be resolved with medication. There is more understanding about how hypothyroidism affects individuals. Even with limitations, our data show a huge difference between hypoPT and hypothyroidism in terms of people attending hospital with a broad array of severe and significant pathologies. It is not an ideal comparison, because we are comparing one group where most patients are taking a replacement hormone with another group that generally are not. However, it does show a stark difference between two chronic diseases that are often confused.

**Giustina:** Under conventional treatment, there is a progressive loss of renal function. More than half of patients develop renal impairments. It is important to think about alternative treatments to protect the kidney. Data published on 5-year follow-up suggest that PTH can have a protective effect on the kidneys compared with standard treatment.

**Bilezikian:** PTH is a polyfunctional hormone, regulating more than one organ or system. We focus on the kidney, skeleton and QoL, but the vascular and cardiovascular effects are not being measured. There are few other hormone deficiency states where we do not replace the missing hormone. We are limited in our assessment of the full effects of conventional or PTH therapy because we are not measuring all the outcomes.

**Gittoes:** It seems counterintuitive that patients could feel well but have abnormal biochemical levels, but if you see enough patients with hypoPT you will observe them fall into these quadrants. There are patients with worryingly low calcium who do not report any neuromuscular symptoms. The 'Frankfurt quadrant' is a helpful tool to subcategorise patients. Managing patients with poor biochemical results but no reported symptoms is challenging. Continuity of care and building a relationship with each patient are important. Pushing too hard could lead to a hypercalcaemic episode. Renal dysfunction could be classified as a co-morbidity or a complication of hypoPT. The important thing is to have tools to intervene to improve patient outcomes.

**Clarke:** There is a challenge in defining adequate control in terms of symptom control, functional control and life experience, even if biochemistry is not at the desired level. Prospective data will help improve the definition of adequate control. Perhaps patients who feel well despite poor biochemical results can be less aggressively managed in future.

## Key learning points

- **Currently, we do not have a clear definition of adequate control in hypoPT**
- **Treatment decisions based largely on biochemistry exclude some longer term complications, so we have an incomplete picture**
- **There is a need for more prospective data on longer term outcomes in hypoPT**

**'We do not have a clear definition of adequate control, which makes it a moving target. Lack of awareness of hypoPT among patients and clinicians results in suboptimal management and unmet need. International guidelines will help to pull the evidence base together, promote awareness and empower patients to demand better care.'**

# Session 2: Management of hypoparathyroidism: special patient groups and circumstances

## Managing patients with hypoparathyroidism during the COVID-19 pandemic

**Karin Amrein** *(Austria)*

Patients with chronic hypoparathyroidism (hypoPT) have increased risk of infection, hospitalisation and mortality compared with individuals without chronic hypoPT.[1] A 2019 population-based study found that patients with hypoPT were two to three times more likely to be admitted to hospital than control subjects.[2]

Multiple predictors for infection have been identified in patients with hypoPT, including elevated phosphate, a higher number of hypercalcaemic episodes and longer duration of disease.[3] The increased risk may be related to deficiency in calcium, which is essential for immune system function.

Results from the Evaluation of Immune Function in Post-surgical and Autoimmune Hypoparathyroidism (EMPATHY) Study showed that patients with chronic hypoPT on conventional therapies had smaller populations of certain immune system cells compared with control subjects.[4] This supports the immunoregulatory role of parathyroid hormone (PTH).

**COVID-19 and hypoPT**

Case reports suggest that hypoPT may emerge secondary to COVID-19-associated respiratory disease. Severe COVID-19 infection was found to be associated with the development of autoantibodies in around 50% of cases.[5] It has also been suggested that COVID-19 infection may unmask pre-existing hypoPT.[6]

Recommendations are to continue existing medication protocols in patients with hypoPT and COVID-19,[7] with careful consideration of sick day rules, given the risks associated with administering too little or too much calcium.

**HypoPT and COVID-19 vaccination**

Anecdotally, there has been some vaccine hesitancy among hypoPT patients. However, both mRNA and vector vaccines have been shown to be highly efficient. With more than seven billion doses administered, the small risks are now known. The risks associated with COVID-19 infection are much greater.

Vaccination against SARS-CoV-2 is highly effective and appropriate for patients with chronic hypoPT.

### Key learning points

- **There is an increased risk of infection and hospitalisation in patients with hypoPT**
- **Calcium and PTH are essential for the immune system**
- **COVID-19 infection can unmask, cause and worsen hypoPT**
- **Vaccination against COVID-19 is very important in patients with hypoPT**

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## Chronic hypoparathyroidism and pregnancy outcomes

**Sigríður Björnsdóttir** *(Sweden)*

There are limited data on pregnancy outcomes in women with chronic hypoparathyroidism (hypoPT). Case reports have shown pregnancy in women with the condition to be associated with significant maternal and fetal morbidity, early fetal loss and preterm delivery.

**Cohort study**

Sweden has high quality population-based registers. The Swedish National Patient Register, the Swedish Prescribed Drug Register and the Swedish Medical Birth Register were used to identify 97 women with chronic hypoPT, who were dispensed active vitamin D at least twice within 13–24 months following first diagnosis, and who gave birth after they had been diagnosed with hypoPT.[1] The Total Population Register was used to identify 1030 age-matched controls. The two groups delivered 139 and 1577 infants respectively, following diagnosis between 1997 and 2017.

Of these women, 76.4% had post-surgical hypoPT and 23.6% had non-surgical hypoPT. Women with chronic hypoPT had more frequent diabetes mellitus and chronic kidney disease (CKD) than the control group.

**Pregnancy outcomes**

After adjusting for diabetes mellitus, CKD, maternal age at delivery and calendar year of delivery, cases of chronic hypoPT were associated with a nearly twofold increased risk of induction of labour and significantly lower infant birth weights, compared with controls.

No difference was found in infant length, size for gestational age or head circumference after adjustments. Mean gestational age at delivery after controlling for diabetes mellitus, CKD and pre-eclampsia was not significantly younger. There was no difference in congenital malformations or perinatal death.

**Management of chronic hypoPT during pregnancy and lactation**

Treatment should aim to avoid both hypocalcaemia and hypercalcaemia in pregnant patients. Serum calcium should be monitored every 3–4 weeks during pregnancy and lactation, and more frequently in the month preceding and following birth. Treatment with thiazide diuretics or parathyroid hormone (PTH) should be avoided. During lactation, a lower dose of calcitriol or calcium may be required.

### Key learning points

- **Most women with chronic hypoPT have normal pregnancy outcomes, but maternal hypoPT is associated with a higher risk of induction and lower infant birth weight**
- **Therapy should focus on avoiding hypocalcaemia and hypercalcaemia in pregnant patients**
- **Serum calcium should be monitored regularly during pregnancy and lactation**

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# Panel discussion: **Adjustments in monitoring and management across the patient journey**

*Expert panel:* **Bart L Clarke** *(Chair, USA),* **Karin Amrein** *(Austria),* **Sigríður Björnsdóttir** *(Sweden),* **Maria Luisa Brandi** *(Italy),* **Andrea Giustina** *(Italy),* **Aliya A Khan** *(Canada)*

**The panel of experts discussed questions from the audience regarding the monitoring and management of patients with chronic hypoparathyroidism (hypoPT).**

### HypoPT, infection and mortality risk

**Khan:** There is an increased risk of infection in patients with chronic hypoPT and hypocalcaemia, but we have insufficient data to say if this is because of hypocalcaemia, low parathyroid hormone (PTH), or a combination of the two. Hypocalcaemia itself does not seem to be associated with an increased risk of infection.

**Clarke:** Calcium is known to play a role in autoimmunity and could also have effects on immune function necessary to fight off infection. The Evaluation of Immune Function in Post-surgical and Autoimmune Hypoparathyroidism (EMPATHY) Study suggested multiple effects on many different aspects of immunity in patients with chronic hypoPT.

**Amrein:** We see hypocalcaemia in severely ill patients regularly. It appears that the more severely ill a patient is with hypoPT, the more severe the hypocalcaemia is. Regarding increased mortality risk, we do not have enough data to say if any specific cause of death is more common in patients with hypoPT.

**Brandi:** It would be helpful to investigate the role of phosphate in mortality, since hyperphosphataemia is very well linked to higher mortality. There may also be a link between immune checkpoint inhibitors and malignancy, which needs to be better understood.

### HypoPT and COVID-19

**Giustina:** From our recent data, it appears that parathyroid function may be affected by COVID-19. Data published during the SARS pandemic found traces of the virus in parathyroid cells. This suggests that parathyroid cells are involved in coronavirus infection.

**Amrein:** It appears that COVID-19 can both unmask latent hypoPT and cause direct parathyroid damage. Two case reports showed new onset non-surgical hyperparathyroidism, caused by acute viral infection. Andrea Giustina has also published a case report where the patient had underlying hypoPT, which was unmasked by the increased demands caused by the acute illness.

**Khan:** We need to emphasise that patients with chronic hypoPT are at greatly increased risk of COVID-19 and, should they develop it, their outcomes may not be as good as someone who is euparathyroid. We need to ensure that these individuals have vaccinations and boosters.

**Brandi:** In the context of the pandemic, we want to maintain calcium balance in patients with hypoPT, but I would not make any recommendation to increase calcium levels. Increasing vitamin D may be another issue.

### HypoPT and pregnancy

**Björnsdóttir:** In pregnant and lactating patients with hypoPT, calcium and vitamin D doses vary considerably. None of us have seen more than a handful of pregnant patients with hypoPT, and the requirements for vitamin D and calcium during pregnancy can differ between different pregnancies in the same woman. In our study involving pregnant patients with chronic hypoPT, we did not have information regarding calcium levels in the infants. We hope to get those data in the future.

**Khan:** When we reviewed pooled data from Canada and Denmark, we found that approximately 20% of pregnant patients required significant adjustment of their active vitamin D and calcium. It emphasises the importance of close monitoring, because we cannot predict which patients will require more active vitamin D or calcium. The new data from Sweden, which show that patients generally do well, are very reassuring for patients. Our new recommendations on hypoPT and pregnancy emphasise the importance of monitoring closely every 2–3 weeks and ensuring that calcium is in the normal range.

**Björnsdóttir:** The positive pregnancy outcomes in Sweden could be related to the good standard of care. An international study could identify differences between countries.

**Brandi:** These findings have also been confirmed in Italy. It would be interesting to monitor bone metabolism during pregnancy.

**Clarke:** The US healthcare system may not be as reliable or precise for follow up and management as that in Sweden. Locally, most patients do very well or even better during pregnancy. Their dose requirements seem to drop in general and complications during labour are rare.

**Khan:** There are two case reports of pregnant women with hypoPT who used PTH during pregnancy, with no untoward effects on the fetus. However, it is not recommended, as there are insufficient safety data.

## Key learning points

- **Patients with chronic hypoPT and hypocalcaemia appear to be at greater risk of infection**
- **Recent data suggest that parathyroid function may be affected by COVID-19, both in terms of unmasking latent hypoPT and causing new onset hypoPT**
- **Patients with hypoPT are at increased risk of COVID-19 and of poor outcomes in case of infection, therefore vaccination is to be encouraged**
- **Pregnant patients with hypoPT should be closely monitored, as calcium and vitamin D doses may need to change, but new data suggest that patients with hypoPT are not at significantly higher risk of poor pregnancy outcomes**

**‘There is an increased risk of infection in patients with chronic hypoPT and hypocalcaemia, but we have insufficient data to say if this is because of hypocalcaemia, low PTH, or a combination of the two.’**

# Session 3: **Moving beyond conventional therapy to decrease adverse effects on organ systems**

## Switching from conventional to hormonal therapy in hypoparathyroidism with chronic kidney disease: a case study

**Polyzois Makras** *(Greece)*

Patients with chronic hypoparathyroidism (hypoPT) have a higher risk of renal complications.[1] In the absence of the calcium-retaining effects of parathyroid hormone (PTH), reduced renal calcium reabsorption may lead to hypercalciuria, nephrocalcinosis and renal dysfunction.[2]

The cause of the chronic renal failure is not established. Conventional therapy corrects calcium levels without affecting renal calcium reabsorption and phosphate excretion. This suggests that renal disease is not a consequence of a lack of PTH action. Treatment with vitamin D may be suboptimal, causing episodes of increased calcium and phosphate products.

The efficacy and safety of PTH(1–84) in patients with hypoPT have been evaluated in a 24-week randomised double-blind controlled trial. Kidney function was shown to remain steady during a period of 72 months.

There are currently no long term, head-to-head clinical trials comparing the effects on renal function of PTH replacement therapy and conventional treatment.

**Case presentation**

A female patient presented with primary hyperparathyroidism in 2001, when she was 56 years old. For the next 16 years, her primary hyperparathyroidism was managed through medications, as the hyperfunctioning parathyroid tissue could not be located. Her disease was complicated by renal stones needing lithotripsy and by osteoporosis, which was treated with bisphosphonates and later denosumab. Calcium levels remained stable.

In 2017, at the age of 72, the patient underwent total thyroidectomy and neck exploration. A parathyroid adenoma, multinodular goitre and two normal parathyroids were excised, resulting in permanent post-surgical hypoPT.

The patient was treated with levothyroxine, denosumab, venlafaxine, alfacalcidol, calcium carbonate, cholecalciferol and magnesium. After switching to recombinant human (rh)PTH(1–84) treatment due to severe fluctuations in calcium levels, she maintained stable calcium homeostasis and her renal function significantly improved.

### Key learning points

- **Conventional therapy corrects calcium levels without affecting renal calcium absorption**
- **No long term head-to-head trials have compared the renal effects of rhPTH and conventional treatment**
- **Long term rhPTH(1–84) treatment seems beneficial in preserving renal function, and safer in hypoPT patients with kidney disease than conventional therapy**

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## Long term outcomes with different approaches to treatment of hypoparathyroidism: the kidney

**Elvira O Gosmanova** *(USA)*

Chronic hypoparathyroidism (hypoPT) adversely affects multiple organ systems, notably the kidney. Parathyroid hormone (PTH) regulates intestinal absorption and renal excretion of calcium. In acute hypoPT, sudden loss of PTH reduces renal absorption of calcium and increases urinary calcium. Plasma calcium concentration rises and falls in parallel with PTH, intestinal calcium absorption and renal calcium excretion.

**Conventional treatment**

Conventional treatment of chronic hypoPT with oral calcium and vitamin D supplementation often leads to increased urinary calcium excretion. It is associated with renal complications, including nephrocalcinosis and nephrolithiasis,[1] an increased risk of chronic kidney disease (CKD) and a higher decline in estimated glomerular filtration rate (GFR).

Increased intestinal calcium absorption during conventional therapy can affect multiple organs, including the central nervous system, the eye and the blood vessels.

**Treatment with rhPTH**

Conversely, treatment with recombinant human PTH (rhPTH(1–84)) may offer renal protection. A prospective study of 24 patients with chronic hypoPT, who were treated with rhPTH(1–84) for 8 years, found that calcium and vitamin D supplementation could be reduced. Albumin-corrected serum calcium, serum phosphate and serum calcium–phosphate product remained within or just below acceptable ranges.[2] Urinary calcium excretion decreased steadily below pretreatment levels, declining by 38% by year 8. Renal function remained stable throughout the entire treatment duration.

Several reports confirmed the stability of renal function in patients with chronic hypoPT who received long term rhPTH(1–84) treatment, compared with those on conventional therapy.[3] Recent results have shown that the risks of incidental CKD and a sustained estimated GFR decline of above 30% were both significantly increased in patients managed with conventional treatment compared with those receiving rhPTH(1–84).[4]

### Key learning points

- **Conventional treatment for chronic hypoPT is associated with adverse effects in the kidney**
- **rhPTH(1–84) reduces the need for calcium and vitamin D supplementation, restores phosphate homeostasis and may improve renal outcomes**
- **Further head-to-head trials are needed to understand how the two treatments affect kidney outcomes**

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# Long term outcomes with different approaches to treatment of hypoparathyroidism: the heart

**Lars Rejnmark** *(Denmark)*

Hypocalcaemia, a common sign of chronic hypoparathyroidism (hypoPT), is known to affect the heart.[1] The effects are usually reversible, if calcium levels are normalised.

Multiple epidemiological studies have demonstrated that chronic hypoPT is associated with increased risk of cardiovascular disease (CVD). A registry study in Denmark found that patients with hypoPT were three times as likely to develop renal insufficiency as those without hypoPT, but found no difference in the incidence of ischaemic heart disease. Later studies have found that patients with non-surgical hypoPT are at greater risk of CVD compared with patients with post-surgical hypoPT.[2,3]

A large scale claims analysis in the USA found that patients with chronic hypoPT had a significantly increased risk of CVD, including coronary artery disease, myocardial infarction, stroke and a combined CVD endpoint, than those without hypoPT.[4]

**Vascular calcification in chronic hypoPT**

Vascular calcification may contribute to the increased CVD risk in patients with chronic hypoPT. In one study, vascular calcification occurred more frequently in patients with either non-surgical or post-surgical chronic hypoPT when compared with control subjects.[5] Patients with lower leg arterial calcifications had higher plasma calcium levels and a lower estimated glomerular filtration rate than those without calcifications.

**The importance of biochemical control**

Failure to achieve and maintain mineral homeostasis is an important determinant of CVD risk. Low levels of ionised calcium, frequent hypercalcaemic episodes and duration of hypoPT have been associated with elevated CVD risk.[6] Levels of phosphate and calcium–phosphate products do not seem to matter.

The risk of CVD appears to be lowered in those treated with replacement parathyroid hormone compared with conventional calcium and active vitamin D supplementation.

## Key learning points

- **The risk of CVD seems to increase in patients with chronic hypoPT, especially in non-surgical cases**
- **CVD risk is associated with low calcium levels, hypercalcaemia and disease duration**
- **Parathyroid hormone therapy may lower CVD risk in chronic hypoPT, though further studies are needed**

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# Hypoparathyroidism: treatment and long term effects on bones

**John P Bilezikian** *(USA)*

Chronic hypoparathyroidism (hypoPT) results in abnormal mineral handling, changes in bone quality and fracture risk.

Less is known about how different treatment approaches affect bone remodelling and structure, as skeletal metabolism has not been included in major studies of chronic hypoPT treatment.

**Treatment approaches**

Conventional treatment of chronic hypoPT involves calcium and vitamin D supplementation. However, this does nothing to address the pathophysiology of absent parathyroid hormone (PTH) or reverse the skeletal abnormalities characteristic of chronic hypoPT. A growing body of evidence has shown that administration of recombinant human PTH (rhPTH(1–84)) can ameliorate changes in bone metabolism and structure.[1]

In patients treated with rhPTH(1–84), bone turnover markers appear to increase rapidly in the first year, before subsiding to a steady, euparathyroid state that is higher than baseline. This suggests that rhPTH(1–84) 'wakes up' the skeleton and normalises bone metabolism to a degree.

Histomorphometric analysis of bone from patients treated with rhPTH(1–84) has also shown marked increases in bone formation markers.[2] Cancellous, endocortical and intracortical bone showed similar changes.

Patients with chronic hypoPT who were treated with rhPTH(1–84) and followed for 8 years showed increased lumbar spine and total hip bone mineral density (BMD), which peaked at 4 and 8 years. Femoral neck BMD did not change, and one-third radius BMD decreased. BMD at all sites was higher than in age- and sex-matched controls.[3] This pattern of bone density changes is typical of PTH treatment for osteoporosis.[4]

Most recently, a study measured skeletal microstructure using high resolution peripheral quantitative computed tomography (HRpQCT) in patients with chronic hypoPT treated with rhPTH(1–84) for 4 years. Total volumetric BMD was reduced at both the radius and tibia, with reductions in cortical, but not trabecular, volumetric bone density.[5] Further analysis will be needed to understand these changes.

## Key learning points

- **Patients with chronic hypoPT treated with rhPTH(1–84) have shown improved skeletal dynamics and BMD changes that match the expected effects of PTH in euparathyroid subjects**
- **Effects on skeletal microstructure have been demonstrated using bone biopsy, trabecular bone score and HRpQCT, but effects on fracture risk remain unknown**

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# What have we learned about the best way to deliver hormonal therapy?

**Bart L Clarke** *(USA)*

A variety of drug delivery options have been developed, or are in development, for hormone therapy in patients with chronic hypoparathyroidism (hypoPT; see the table below). Of these, subcutaneous and oral administration are most prominent.

**Effect of rhPTH(1–84) on need for supplementation**

Recombinant human parathyroid hormone (1–84) (rhPTH(1–84)) is approved for the treatment of chronic hypoPT. A randomised controlled trial including 134 patients with chronic hypoPT showed that subcutaneously administered rhPTH(1–84) reduced the requirement for calcium and vitamin D supplementation and was well-tolerated.[1]

Potentially, multiple daily dosing might lead to more stable serum calcium or a quicker reduction in urinary calcium, though it could lead to reduced compliance and would probably need more frequent monitoring with a calcium meter. However, a comparison of rhPTH(1–84) delivery once daily (100µg) or twice daily (25 or 50µg), with or without calcium, showed that the only notable difference between dosing regimens was an incremental reduction in urinary calcium excretion in the twice daily regimen compared with single dosing, but this was lessened when treatment included supplemental calcium.[2]

**TransCon PTH(1–34)**

Another approach under investigation is pegylated TransCon PTH(1–34). This modified molecule allows slow release of PTH(1–34) into the circulation by time-, temperature- and pH-dependent cleavage of a linker.

Administration of TransCon PTH(1–34) to patients with chronic hypoPT has been shown to decrease dependence on vitamin D and calcium supplementation, decrease urinary calcium, and normalise calcium, phosphate and serum phosphate product.[3]


**Other delivery options**

Approaches under development include long-acting PTH and PTH analogues, which involve various modifications of the PTH molecule, or the inclusion of carriers such as albumin and targeting agents.

Orally administered PTH(1–34) is in development for treatment of both hypoPT and osteoporosis. Sequestering of oral PTH(1–34) in a nanocarrier has been investigated as a potential route for delivery via the enterohepatic circulation. Chitosan and silk fibroin microparticles may allow stable and sustained release of rhPTH molecules into the intestinal circulation.

Transdermal PTH delivery using rapidly dissolving microneedle arrays may also be an option.

In these ways, multiple preparations of PTH are being developed, each with unique kinetics and pharmacodynamics, which will be difficult to predict before human trials. One method may eventually achieve good results with greater convenience.

| Current and future possible options for hormone therapy delivery in hypoPT that is not well controlled. |
|---|
| rhPTH(1–84): s.c. preparation[4] |
| rhPTH(1–34): s.c. or oral preparation[5,6] |
| TransCon PTH(1–34)[3] |
| rhPTH(1–84) or PTH(1–34) by pump infusion[7,8] |
| PTH by patch or implantable microchip[9,10] |
| Nasal spray PTH(1–34)[11] |
| Other PTH analogues: e.g. LY627-2K, other long-acting PTH preparations[12–14] |
| Small molecular PTHR1 agonists: CH5447240 after PC0371 discontinued[15] |
| Microencapsulation of parathyroid cells[16] |
| Stem cell therapy[17] |
| Parathyroid gland transplantation[18] |

## Key learning points

- **Multiple preparations of PTH are being developed for the treatment of chronic hypoPT and osteoporosis**
- **Other PTH analogues may eventually achieve similar results, with greater convenience**
- **More research will be needed to understand pharmacokinetic/pharmacodynamic differences among various PTH preparations**

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# Guidelines for hypoparathyroidism: what's new?

**Aliya A Khan** *(Canada)*

A Second International Workshop has been convened over the last 2 years to develop new evidence-based guidelines on the diagnosis, evaluation and management of parathyroid disease. Four taskforces addressed issues pertaining to the diagnosis, prevention, evaluation and management of hypoparathyroidism (hypoPT). The outcomes of this work will be published in *Journal of Bone & Mineral Research* in due course.

Systematic reviews and meta-analysis were carried out to develop graded recommendations regarding the complications and management of hypoPT. In addition, narrative reviews were completed regarding the epidemiology, financial burden and aetiology of the disease.

**Symptoms and complications of hypoPT**
The first systematic review addressed the symptoms and complications of chronic hypoPT. A total of 81 studies met the criteria for inclusion. The most common symptoms and complications were found to include cataract, infection, nephrocalcinosis or nephrolithiasis, renal insufficiency, seizures, depression, ischaemic heart disease and arrhythmia.

**Optimal monitoring strategies**
Given that only two papers were identified for the second systematic review, a current practice survey of more than 100 panel members was undertaken. The panel's practices for monitoring hypoPT complications include the following.

Initial assessment:

- measure serum creatinine, calcium, magnesium, phosphate and vitamin D
- measure 24-hour urine for creatinine (or creatinine clearance) and calcium.

Follow-up monitoring:

- in stable patients, monitor creatinine, calcium, phosphate and magnesium every 12 months, monitor vitamin D every 6–12 months, and monitor 24-hour urine testing for calcium and creatinine clearance every 6 months to 2 years
- in non-stable patients, frequently monitor serum calcium and phosphate measurements, as clinically indicated.

The panel also suggest completing a baseline assessment for the presence of renal calcifications or stones, and monitoring serum calcium within days of a change in medical treatment. Dose recommendations for conventional therapy have also been included.

**Consequences of PTH versus conventional therapy**
Only six studies met the inclusion criteria for the third system review and meta-analysis, with some limitations. In most studies, eucalcaemia was maintained with parathyroid hormone (PTH) therapy. In some studies, PTH treatment led to a decline in urinary calcium. PTH therapy was found to reduce serum phosphorus, but also to lead to more episodes of hypercalcaemia. This was probably an effect of study design.

Conventional therapy was found to have no impact on quality of life (QoL). QoL improved slightly with PTH therapy.

PTH was clearly effective in allowing a 50% or greater reduction in doses of activated vitamin D and calcium, which is significant, as patients have difficulty tolerating high doses of calcium and this will therefore make treatment much easier.

PTH was associated with a small increase in adverse events, generally limited to a higher incidence of hypercalcaemia.

**Graded recommendation**
In patients with chronic hypoPT, the panel suggests conventional therapy as the first-line treatment. When conventional therapy is deemed unsatisfactory, the panel considers use of PTH. Longer and larger studies with patient important outcomes are required.

**Ungraded recommendations**
In patients with hypoPT, the panel proposes:

- treatment with calcium and activated vitamin D, with the goal of achieving serum calcium just below or in the lower half of the normal reference range (though international practice differs)
- alleviating symptomatic hypocalcaemia while avoiding hypercalcaemia
- avoiding hypercalciuria
- avoiding hyperphosphataemia
- treating to normalise plasma magnesium levels
- aiming for vitamin D levels in the normal range
- considering treating hypercalciuria with thiazide diuretics in conjunction with a low salt diet
- considering PTH replacement therapy in patients who are not well controlled on conventional therapy.

**Calcium homeostasis during pregnancy**
Consensus recommendations on calcium homeostasis in pregnancy and lactation have recently been published.[1] Changes in mineral homeostasis during pregnancy usually result in lower dose requirements for calcium and active vitamin D metabolites.

Treatment should focus on ensuring that the mother receives adequate calcium supplementation. Both hypocalcaemia and hypercalcaemia in pregnancy can have consequences for the fetus. The panel proposes close monitoring of pregnant and lactating patients with hypoPT.

**Emerging hypoPT therapies**
Emerging therapies include long acting PTH analogues, PTH receptor 1 agonists, calcilytics which increase PTH and renal calcium reabsorption, and TransCon PTH.

## Key learning points

- **Reports from the Second International Workshop on Parathyroid Disorders will be published in *Journal of Bone & Medical Research* in due course**
- **In relation to hypoPT, systematic reviews and meta-analysis have covered symptoms and complications, optimal monitoring strategies, and consequences of conventional therapy compared with PTH therapy, with graded and ungraded recommendations**
- **Specific recommendations have been made for the management of pregnant patients with hypoPT**

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# Panel discussion: **Anticipating outcomes – experts' perspectives**

*Expert panel:* **Bart L Clarke** *(Chair, USA)*, **John P Bilezikian** *(USA)*, **Elvira O Gosmanova** *(USA)*, **Aliya A Khan** *(Canada)*, **Polyzois Makras** *(Greece)*, **Claudio Marcocci** *(Italy)*, **Lars Rejnmark** *(Denmark)*

**The panel of experts discussed questions and themes relating to future outcomes in the treatment and management of hypoparathyroidism (hypoPT).**

### HypoPT and renal outcomes

**Gosmanova:** There have been no clinical trials evaluating the use of additional therapies to reduce the risk of chronic kidney disease (CKD) progression in patients with chronic hypoPT. Normal guidelines would apply, such as control of blood pressure and co-morbidities, paying close attention to hyperphosphataemia and hypercalciuria.

One important marker of CKD is 24-hour urinary calcium excretion. Changes in urinary calcium excretion in patients with chronic hypoPT and CKD have not been studied. In the general population, calcium excretion tends to decline as CKD progresses. Patients with more stable calcium levels have less chance of developing CKD or CKD progression. Achieving steady calcium control may result in better outcomes. Data on this will be published shortly.

**Bilezikian:** Fluctuations in urinary calcium seen in the long term study of parathyroid hormone (PTH) replacement are probably due to the use of a single 24-hour urine calcium measured once a year, over 8 years. Overall, a reduction in urinary calcium excretion was seen in patients treated with PTH, though it may be time-dependent.

**Gosmanova:** 24-hour urinary calcium excretion is probably still the gold standard in assessing calcium excretion. However, it can be impractical and prone to errors. Urinary spot calcium to creatinine ratio is a very attractive option, but those calculations do not account for degree of kidney function.

**Marcocci:** Hypercalcaemia has been shown to be more common in those with calcium levels below the median. Conventional treatment for chronic hypoPT may be considered suboptimal, because patients have symptomatic hypercalciuria. Most data on complications cover patients treated between 2000 and 2015, so we can expect recent improvements in patient management to result in a lower rate of complications in future.

### HypoPT and skeletal outcomes

**Bilezikian:** A meta-analysis has shown an increase in risk of vertebral fractures among those who have non-surgical chronic hypoPT, which suggests that there is a skeletal phenotype of this disease. Low bone density and osteoporosis seen in those with chronic hypoPT may be postmenopausal or related to other aetiologies of bone loss. The observation should not be dismissed. We should think about the therapeutics of low bone density in the context of chronic hypoPT.

**Khan:** We will consider adding a statement to the new guidelines about the risk of reduction in serum calcium with certain therapies.

### HypoPT and cardiovascular outcomes

**Rejnmark:** Patients with non-surgical hypoPT seem to have a higher incidence of cardiovascular disease (CVD), compared with controls, than do patients with post-surgical disease. That may be due to diagnostic delays in patients with non-surgical hypoPT. We do not have enough data to explain the components that contribute to cardiovascular morbidity. Increased arterial stiffness has been observed in cross-sectional studies, but more data are needed before considering this as an additional risk score for CVD in chronic hypoPT.

**Rejnmark:** Regarding the risk of ischaemic heart disease in patients with post-surgical chronic hypoPT, our major problem is small cohorts, leading to variable results. We need more longitudinal data.

**Khan:** The meta-analysis done during the preparation of the guidelines has several clinical implications, particularly around reducing pill burden. We need more data to answer the long term questions around prevention of renal and cardiovascular complications, infections and quality of life. The meta-analysis shows us that we need to persist with PTH therapy.

### Interpretation of 'unsatisfactory' control in hypoPT

**Khan:** The guidelines taskforce was unanimous in the view that wide fluctuations in serum calcium are what marks an unsatisfactory response to conventional therapy. We encourage endocrinologists to monitor phosphate, urine, calcium and renal impairment. If patients have renal impairment, we need to preserve remaining renal function. These patients are very suitable for switching to PTH therapy.

**Bilezikian:** We use terminology such as 'controlled' and 'not well controlled'. Perhaps the guidelines should include the term 'unsatisfactory', to clarify what we mean by 'poor control'.

### Future developments

**Clarke:** The best approach to PTH delivery will be the one that is easiest, is least expensive, and minimises the risk of side effects. No single preparation meets all these objectives yet. New data from injectable TransCon PTH suggest it may work better than intravenous PTH. It will be 5–10 years before we determine the best approach.

**Khan:** We also need to have better means of measuring real-time calcium. This will help to reduce the incidence of hypercalcaemia and hypocalcaemia by giving patients more control. A portable calcium meter is available in Canada, but it needs further refinement for patient use.

**Makras:** In Greece, an algorithm has been proposed for the treatment of chronic hypoPT, to support guidelines for blood and urine measurements and doses for calcium carbonate and alfacalcidol. Calcitriol is unavailable. The Greek guidelines are very similar to the European Society of Endocrinology and international guidelines.

## Key learning points

- **Knowledge is advancing in every area, but many questions remain**
- **The new international guidelines should lead to changes in clinical practice, and confirm the need to pursue PTH therapy**
- **Achieving steady calcium control is essential to minimise the risk of renal complications, and 24-hour urinary calcium excretion remains the gold standard measurement**
- **Evidence suggests that there is a skeletal phenotype of chronic hypoPT, and bone density loss should factor in therapeutic decisions**
- **Patients with chronic hypoPT are at greater risk of CVD, though more data are needed to explain causal factors**

# Concluding comments from GESH 2021

- Hypoparathyroidism is no longer a forgotten rare disease
- With more data, more clinical studies, and more contributions from experts outside the field of endocrinology, momentum is building that will lead to improvements in clinical practice
- However, many questions remain unanswered, which can only be addressed through considerable effort by the community
- The data presented in this Summit demonstrate the value added by different types of study in answering incremental questions
- It is extremely useful to hear about different approaches to practice in different countries
- The latest practice will be reflected in the new international guidelines on hypo- and hyperparathyroidism.

European Society of Endocrinology