

Insight

2020 Number 1

ISSN 2057-4312 (print)
ISSN 2057-3286 (online)

3rd European Symposium on Hypoparathyroidism. Clinical aspects for diagnosing and achieving disease control in chronic hypoparathyroidism **Athens, Greece** **8-9 November 2019**

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Meeting Co-Chairs:

Professor John Bilezikian (USA)

Dr Andromachi Vryonidou-Bompota (Greece)

Meeting Faculty:

Professor Karin Amrein (Austria)

Dr Sigridur Björnsdóttir (Sweden)

Professor Jens Bollerslev (Norway)

Professor Bart L. Clarke (USA)

Professor Volker Fendrich (Germany)

Professor Neil Gittoes (UK)

Dr Peter Kamenický (France)

Assoc. Professor Kalliopi Kotsa (Greece)

Mr Tom Kurzawinski (UK)

Professor Salvatore Minisola (Italy)

Professor Leif Østergaard (Denmark)

Professor Heide Siggelkow (Germany)

Dr Tanja Sikjaer (Denmark)

Dr Symeon Tournis (Greece)

Dr Line Underbjerg (Denmark)

Dr Maria Yavropoulou (Greece)





Welcome to the 3rd European Symposium on Hypoparathyroidism: Clinical aspects for diagnosing and achieving disease control in chronic hypoparathyroidism.

Athens, Greece, 8-9 November 2019

On behalf of the scientific planning committee, we are pleased to provide European Society of Endocrinology members and the wider international community with summary highlights of this event.

As the birthplace of Hippocrates, widely described as the father of modern medicine, Greece was a fitting place to educate more than 100 international delegates on managing patients with chronic hypoparathyroidism (hypoPT). Today, our Greek colleagues are very active in the area of hypoparathyroidism through their development of management guidelines, translating the ESE hypoPT patient medical alert card into Greek and beginning a patient registry.

Our scientific programme of keynote presentations, plenary talks, workshops and round table discussions covered a variety of hypoparathyroidism topics:

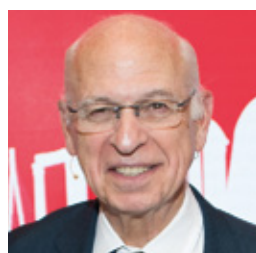
- The importance of parathyroid hormone (PTH) in mineral homeostasis
- Understanding the characteristics of inadequately controlled hypoPT patients
- Obtaining good biochemical control to avoid complications and co-morbidities
- The new evidence that is helping facilitate improvements to management
- How translating current treatment goals and guidelines can improve outcomes for patients.

There are many individuals to thank for helping make this event a success again. First to ESE for writing, publishing and distributing this independent report, through the combined efforts of Dr Rachel Arthur and Nik Screen. Second, we thank Takeda for its support of the educational event and the distribution of the report. Finally, we thank the invited faculty and attendees for their thought-provoking contributions that made the event so educational and memorable.

We hope that ESE readers find that the report expands their own knowledge on the management of patients with hypoparathyroidism.



Meeting Co-Chairs:



Professor John Bilezikian
Columbia University Medical
Center, New York, USA



**Dr Andromachi
Vryonidou-Bompota**
Red Cross Hospital,
Athens, Greece

Insight

This meeting report has been commissioned and published independently by the European Society of Endocrinology for the continuing education of ESE members, affiliate Society member and other health care professionals. The views expressed by the contributors are not necessarily those of ESE. This content focus around Calcium and Bone reflects the strategy to provide Society activity and services organised around eight specialised areas. To learn more about our continuing ESE parathyroid disorders educational programme (PARAT), please visit www.eese-hormones.org/parat.

Project delivery on behalf of ESE:

Editorial review: Dirk de Rijdt, Vicki di Guisto

Independent Medical Writer: Dr Rachel Arthur

Publishing Project Management: Nik Screen, Versatility

Design and production: Qube Design Associates

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Takeda has initiated and funded the 3rd European Symposium on Hypoparathyroidism; Clinical aspects for diagnosing and achieving disease control in chronic hypoparathyroidism. 8-9 November 2019, Athens, Greece. The Scientific Planning Committee for this event (SPC) is comprised of specialists who provide scientific and planning oversight for the overall program and content. Its members are recognised authorities in the field of endocrinology, and they receive an honorarium from Takeda for this work. The highlights of this symposium reflect the scientific opinions of the individual presenters and may not necessarily reflect the opinions of Takeda, or any of its subsidiaries, partners or employees. The publication and distribution of the Insight report on the 3rd European Symposium on Hypoparathyroidism have been made possible by an unrestricted grant from Takeda. A member of the SPC has reviewed Insight Vol 1 2020 to ensure its content accurately reflects the presentations and discussions of the meeting. Takeda have reviewed the content for medical accuracy and for regulatory compliance of medical literature only. Takeda have had no input into its content or publication, nor influenced who it has been distributed by ESE.



We are indebted to the following faculty for providing their expert insights in plenary and keynote presentations, or by chairing and moderating our workshops and panel discussions.



Karin Amrein
Medical University of Graz,
Austria



Professor John Bilezikian
Columbia University
Medical Center, New York,
USA



Dr Sigridur Björnsdóttir
Karolinska University,
Stockholm, Sweden



Professor Jens Bollerslev
Oslo University Hospital,
Norway



**Dr Andromachi
Vryonidou-Bompota**
Red Cross Hospital, Athens,
Greece



Professor Bart L. Clarke
Mayo Clinic, Rochester,
USA



**Professor Volker
Fendrich**
Schöen Klinik, Hamburg,
Germany



Professor Neil Gittos
University of Birmingham,
UK



Dr Peter Kamenický
Paris-Sud University,
France



**Assoc. Professor
Kalliopi Kotsa**
Aristotle University of
Thessaloniki, Greece



Mr Tom Kurzwinski
University College
Hospital, UK



**Professor Salvatore
Minisola**
Sapienza University of
Rome, Italy



**Professor Leif
Østergaard**
Aarhus University Hospital,
Denmark



**Professor Heide
Siggelkow**
University Medical Centre,
Göttingen, Germany



Dr Tanja Sikjaer
Aarhus University Hospital,
Denmark



Dr Symeon Tournis
University of Athens,
Greece



Dr Line Underbjerg
Aarhus University,
Denmark



Dr Maria Yavropoulou
University of Athens,
Greece



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The clinical presentation of HypoPT patients and the importance of PTH in mineral homeostasis

Speaker: Dr Maria Yavropoulou (Greece)

The opening keynote presentation was given by Dr Maria Yavropoulou (Athens, Greece).

The PTH molecule

PTH is synthesised by the parathyroid glands as a precursor molecule of 115 amino acids but then processed to a mature protein of 84 amino acids. The N terminal is responsible for many classic biological actions involved in binding to the receptor (Murray 2005); the functions of the middle portion and C terminal are not well understood but they may have their own biological functions and receptors.

There is negative feedback regulation of PTH secretion by calcium; parathyroid cells are very sensitive in order to maintain serum calcium in a very narrow normal range.

PTH and calcium levels may be increased or decreased in different conditions (Khairallah 2007). In primary hyperparathyroidism PTH levels and calcium levels are increased. In hypoparathyroidism the levels of PTH and calcium are decreased, and in hypercalcemia due to malignancy there are increased calcium levels but very low suppressed PTH levels. PTH is the hormone that regulates the level of $1,25(\text{OH})_2$ vitamin D, and vitamin D can actually suppress PTH excretion.

Cellular actions of PTH

The cellular actions of PTH are to increase serum calcium levels through the three main target organs—bone, kidney and intestinal mucosa. PTH has an effect on every type of cell in bone tissue; on osteoblasts, osteoclasts and osteocytes as well, and regulates lineage allocation in the bone marrow.

In the kidneys, PTH has an effect on tubular handling of calcium, phosphate, magnesium, sodium and amino acids plus production of $1,25(\text{OH})_2$ vitamin D.

Hypoparathyroidism is a rare and complex condition that results in disrupted mineral homeostasis (Bilezikian 2011). It is characterised by absent or inappropriately low levels of endogenous PTH in association with hypocalcemia and hyperphosphatemia. When we refer to permanent hypoparathyroidism after surgery, this is defined as low calcium and PTH levels at least 6 months after surgery. Non-surgical HypoPT can be autoimmune or genetic.

Post-surgical cases are more common than non-surgical cases; it occurs in about 24–37 cases per 100,000 person-years.

Aetiology of HypoPT

The most frequent cause of HypoPT is surgical removal or loss of viability of parathyroid glands: it accounts for up to 80% of cases. Up to 4.6% of patients develop permanent HypoPT, defined as persisting for 6 months after surgery. It is mostly seen in patients who have thyroidectomies performed for thyroid or parathyroid cancer, when central neck dissection increases the risk of HypoPT (Giordano 2012).

Non-surgical and syndromic genetic causes of HypoPT include autoimmune APS, DiGeorge syndrome, mitochondrial disorders and HypoPT-retardation-dysmorphism syndrome.

Clinical manifestations

The clinical features of HypoPT are mostly due to hypocalcemia, which can be of acute or more gradual onset depending on the cause (Mannstadt 2017). Chronic hypocalcemia together with chronic hyperphosphatemia drives the disposition to ectopic calcification. Patients can develop extrapyramidal signs, such as Parkinsonism but cataracts are much more common. There are clinical signs of latent tetany.

These patients have problems in various organs. Mitchell (2012) demonstrated that HypoPT patients have a greater decrease in kidney function with ageing compared with age-matched norms as measured by percentages of patients with GFR <60 ml/min. In this cohort 41% of HypoPT patients had kidney disease between stage 3 and 5, and from those approximately 30% had nephrolithiasis and nephrocalcinosis.

Other co-morbidities occur with an increased prevalence in patients with HypoPT (Bollerslev 2015). They include infections, seizures, depression, impaired quality of life, muscle stiffness and pain, and ischaemic heart disease. Although many co-morbidities are observed in post-surgical and non-surgical HypoPT, there are differences between these two groups of patients. The duration of disease is another factor.

Quality of life

This is another important issue in HypoPT patients. Many studies have addressed this parameter using different scores. As an example, quality of life was impaired in Norwegian patients with HypoPT compared with controls in all 8 dimensions measured by the SF-36 scale (Astor 2016). An interesting

large survey was carried out in patients who identified themselves as HypoPT (Siggelkow 2018) but said they were adequately controlled. The impact of HypoPT on daily life was assessed in a symptoms diary: it showed that the ability to exercise was impaired in 89%, sleep was impaired in 85%, ability to work in 80% and family relationships were impaired in 72%.

The management of HypoPT is complex, requiring an individualised approach. A majority of our patients, especially those with some reserve function of the parathyroid glands, can be treated with calcium and active vitamin D metabolites.

Conclusion

HypoPT is a PTH deficiency state characterized by its hallmark, hypocalcemia. The goals of management include not only normalization of the serum calcium but management of associated co-morbidities such as quality of life.

Organ	Comorbidity
Renal	<ul style="list-style-type: none"> • Renal stone disease and impaired renal function • Renal calcifications
Immunological	<ul style="list-style-type: none"> • Infections
Neuropsychiatric	<ul style="list-style-type: none"> • Neuropsychiatric diseases • Seizures • Depression • Impaired quality of life
Musculoskeletal	<ul style="list-style-type: none"> • Muscle stiffness/pain • Proximal humerus fractures*
Cardiovascular	<ul style="list-style-type: none"> • Ischaemic heart disease*
Central Nervous System	<ul style="list-style-type: none"> • Intracerebral calcifications*
Eyes	<ul style="list-style-type: none"> • Cataract*

Fig 1. Comorbidities may occur with an increased prevalence in patients with hypoPT

(*An increased risk has only been documented in non-surgical hypoPT. Adapted from Bollerslev et al 2015)



The importance of biochemical control in HypoPT

Speaker: Dr Line Underbjerg (Denmark)

Dr Line Underbjerg (Aarhus, Denmark) gave a plenary talk on the importance of biochemical control in hypoparathyroidism. The current European guidelines (Bollerslev, 2015) on the management of chronic HypoPT and the avoidance of complications contain recommendations on serum calcium, 24-hour urinary calcium excretion, serum magnesium and phosphate levels, serum calcium-phosphate product (CPP) and vitamin D levels.

Only a few studies have examined the biochemical findings as predictors of risk of complications in patients with either non-surgical HypoPT or post-surgical HypoPT. In a study from Boston, Mitchell and colleagues (Mitchell, 2012) investigated 120 patients with HypoPT and they saw that episodes of hypercalcaemia may be associated with an increased risk of renal insufficiency, and that there might be an association between the duration of disease and risk of complications.

The association between biochemical findings, treatment regimes and risk of complications in patients with HypoPT (both non-surgical and post-surgical) was examined in Denmark, making use of the registries there (Underbjerg 2018). The design was a case control study nested within the cohort of patients with HypoPT living in the region. Cases were defined as patients with HypoPT who had the complication in question, and controls as patient with HypoPT without that complication.

Investigation method

The central database contains lab data from 1994 to 2014. Biochemical results were retrieved for 431 patients with HypoPT. Plasma ionised calcium, plasma phosphate, plasma creatinine and urinary calcium levels were recorded, and from these values the estimated glomerular filtration rate (eGFR) and the calcium-phosphate product (CPP) were calculated.

The risk factors included in the study were plasma ionised calcium, plasma phosphate, calcium-phosphate product, plasma creatinine, episodes of hypercalcaemia, duration of disease and the daily dose of calcium/alfacalcidol. The outcomes examined were mortality, cardiovascular disease (ischaemic heart disease and stroke), renal disease (renal stones and insufficiency) and infections leading to hospitalisation.

Baseline characteristics

Of the 431 patients 351 (81.4%) were female. Age at diagnosis was 41 years, and median duration of disease was 12.7 years. Not surprisingly, the duration of disease was longer in patients with non-surgical HypoPT. At the time of follow-up 86% were still alive; median BMI was normal. 8.4% had diabetes mellitus and 3.5% had hypertension according to ICD codes. Post-surgical HypoPT was the aetiology in 380 patients (88.2%). The majority of patients were receiving both calcium supplements (95%, average dose 1,000mg/day) and alfacalcidol (94%, average dose 1 microg/day).

Biochemical characteristics

The plasma ionised calcium was just below the Danish reference range (1.18 mmol/L), showing that according to this guideline the patients were well controlled. Plasma phosphate was within the reference range; calcium-phosphate product was well below the recommended cut-off, at 2.8mmol²/L². There were 9 patients with ionised calcium, 26 patients with phosphate level and 2 patients with CPP above the upper limits of normal (ULN), thus this cohort of patients in these other ways were also well controlled.

Nearly half (41%) of patients experienced at least one episode of hypercalcaemia, 13% experienced 4 or more episodes, and one patient experienced 18 episodes.

Predictors of mortality

Dose of calcium supplements and alfacalcidol did not have a significant effect on mortality. Patients with phosphate levels and CPP above the median had a significantly higher (more than four-fold) risk of dying; those with duration of disease above the median (12.7 years) had a three-fold risk of dying. Patients in the highest phosphate tertile and highest CPP tertile had an elevated risk compared to those in the lowest tertile, as did those with the longest duration of disease.

Risk of complications

Looking at cardiovascular risk, comparing values above and below the median, duration of disease was the only factor that was associated with elevated risk. Examining the results by tertiles, and using the middle tertile as reference, patients in both the upper and lower tertile for serum ionised calcium had increased risk of cardiovascular disease. Findings for phosphate and CPP were not significant. Patients with a large number of hypercalcaemic episodes and with a long duration of disease had greater risk of CVD.

With regard to renal insufficiency, one third had normal eGFR above 90mL/min, 45% had an eGFR between 60 and 90, and 21% had an eGFR below 60. The Mitchell study found that 41% of their patients had an eGFR below 60 mL/min.. These Danish data are comparable with data from Norway, where 18% of their patients had an eGFR below 60 mL/min. Alfacalcidol doses above the median might protect the patient from renal disease (stones and insufficiency). Patients with CPP above the median had a higher risk of renal disease (approximately double) compared to those with CPP below the median, and again long duration of HypoPT predicted development of renal disease. CPP plus the number of hypercalcaemic episodes plus duration of disease in the highest tertile doubled or tripled the risk of renal disease.

The risk of any infection leading to hospitalisation was assessed. A high plasma phosphate indicated a higher risk of any infection (adjusted OR 1.77) and upper airway infections (adjusted OR 4.44). Patients in the upper tertile for phosphate had more than twice the rate of admission to hospital for infections. Alfacalcidol dose above 1 mcg per day had a protective effect against infections. Number of hypercalcaemic episodes in the highest tertile and duration of disease in the middle tertile were associated with double the risk of hospitalisation for infection.

The conclusions are summarised in figure 2.

21% of patients had renal insufficiency (eGFR <60 mL/min)

Increased Phosphate/CPP:

- ↑ Mortality
- ↑ Infections
- ↑ Renal diseases

Increased number of hypercalcaemia episodes

- ↑ Mortality
- ↑ Infections
- ↑ Cardiovascular disease
- ↑ Renal diseases

Reduced Ionised calcium:

- ↑ Cardiovascular disease

Treatment with high doses of active vitamin D

- ↓ Mortality
- ↓ Renal disease
- ↓ Infections

Fig 2. Complications in hypoPT are closely related to biochemical disturbances

(Data taken from Underbjerg 2018)



The importance of the kidneys in mineral homeostasis

Speaker: Dr Symeon Tournis (Greece)

Dr Symeon Tournis (Athens, Greece) discussed the importance of the kidneys in mineral homeostasis. The kidneys play a major part along with the parathyroids in the metabolism of calcium and phosphate.

Hormonal regulation

The main action of calcitriol is to stimulate absorption of calcium and phosphate from the gut (Eaton 2013). It also influences calcium and phosphate reabsorption from the distal convoluted tubule of the kidney and is important in the maintenance of normal bone remodelling. Finally, calcitriol is very important in suppressing PTH synthesis and it increases the production of FGF23 by osteocytes.

PTH is important for the transfer of calcium and phosphate from bone: it stimulates transfer and stimulates bone resorption. It increases the renal excretion of phosphate at the proximal renal tubule and also it stimulates the reabsorption of calcium at the distal tubule. Also it is important for the activation of vitamin D. Finally, FGF23 is produced by mature osteoblasts and osteocytes: it increases the renal excretion of phosphate. There is a close cross-talk between these three hormones.

Hypoparathyroidism

In cases of HypoPT, with decreased endogenous production of PTH, mineral homeostasis is impaired (Shoback 2008, Vetter 2002). This has effects on bone, with decreased bone turnover and remodelling and decreased release of calcium and phosphate from the bone. The decrease in PTH levels also leads to reduction in the activation of vitamin D leading to low or low-normal levels of $1,25(\text{OH})_2$ vitamin D leading to reduction in calcium and phosphate absorption by the gut. There is also decreased calcium and magnesium reabsorption, and increased phosphate reabsorption, by the kidneys.

Renal co-morbidities in HypoPT

Nephrolithiasis and nephrocalcinosis are important complications in patients with HypoPT. Mitchell (Mitchell, 2012) reported nephrocalcinosis in 31.5% of cases whereas in a study in Italy (Meola, 2018) 30% had renal calcifications. Concerning hypercalciuria, one of the main problems with the data is 24-hour urine excretion is only measured in a minority of patients. In a study (Meola 2018) from Italy of 90 cases of post-surgical and non-surgical HypoPT, about 55% of cases had elevated urinary calcium levels while the study from Boston (Mitchell 2012) showed about 37% and a recent study from Belgium (David 2019) involving 170 patients showed that 36% of

patients had elevated urinary calcium levels. Renal excretion of calcium is believed to be closely related to the renal complications in patients with HypoPT.

Data from a large USA corporate claims database (Chen, 2019), looked at 8,000 HypoPT patients and 40,000 non-HypoPT patients over 5 years of follow-up. The risk of nephrolithiasis seemed to be 80% higher in patients with HypoPT.

Concerning chronic kidney impairment, defined as low eGFR below 60 ml/min, the data is also disturbing. There seems to be an increased frequency of chronic kidney disease in patients with long-term HypoPT. In a study from Denmark (Underbjerg, 2018), 21% of patients had chronic kidney disease. The study from Italy (Meola 2018) gave a 12% incidence of chronic kidney disease and in Mitchell's study (Mitchell, 2012) 41% of patients had chronic kidney disease as defined by low eGFR. Even at the age of 40-60 years there is increased prevalence of chronic kidney disease in patients with HypoPT.

It seems that all aspects of kidney disease are increased in patients with HypoPT. The risk of renal disease is about 3-4 times higher; the risk of renal insufficiency is 3 times higher in post-surgical and 6 times higher in non-surgical HypoPT; the risk of renal failure is twice as high in post-surgical and 8 times higher in non-surgical HypoPT; and the risk of renal stones is 4 times higher in post-surgical HypoPT.

- Duration of disease
- Hypercalcaemic episodes
- Elevated CPP

Possibly

- Hypercalciuria

Fig. 3 Risk factors for renal complications

First, it is well established that longer duration of disease is associated with an increased prevalence of kidney problems in patients with HypoPT. The number and probably the duration of hypercalcaemic episodes is another risk factor. An elevated CPP is a risk factor for adverse outcomes. The risk appears to be reduced by high doses of alfacalcidol over 1 microgram per day. Most studies have not found that higher urinary calcium is closely associated with kidney stones in patients with HypoPT.

In one study (Curhan 2008), weight-adjusted 24-hour urinary calcium excretion was significantly higher in patients with renal



Kidney Stones (©Shutterstock)

calcification but no correlation was found between serum and urinary levels of calcium and the presence of renal calcification. Most studies failed to find significant associations between high 24-hour urinary calcium excretion and nephrolithiasis.

Calcium supplementation

What is the role of calcium supplementation in renal function? Treatment with calcium salts, especially in higher doses, raises concerns for unwanted complications such as G-I side effects. Patients with HypoPT are predisposed to hypercalciuria when taking calcium or activated vitamin D supplements. For patients with hypercalciuria, clinicians should try to reduce sodium intake and also increase fluid intake. Attempts might be made to reduce the dose of calcium supplements or distribute the doses evenly and also have a trial with thiazide diuretics.

Conclusions

Patients with chronic HypoPT are at increased risk for renal co-morbidities including nephrocalcinosis, renal stones and chronic kidney disease as compared with the general population. It seems that longer duration of disease, increased CPP and hypercalcemia are associated with increased risk of renal disease. 24-hour urinary calcium should be monitored regularly, at least annually, and also imaging of the kidneys should be performed as clinically indicated. It would be wise to have a baseline assessment with renal ultrasound when a patient with HypoPT is first seen and also if the patient has hypercalciuria to decrease sodium and increase fluid intake, reduce the dose of calcitriol and try thiazide diuretics.

“Patients with chronic HypoPT are at increased risk for renal co-morbidities”



Patient cases with compromised biochemical parameters

Moderators: Professor Karin Amrein (Austria) and Dr Symeon Tournis (Greece)

Workshop 1 considered patient cases with compromised biochemical parameters. The first speaker was associate professor Karin Amrein from Graz, Austria. Long-term complications in patients with hypoparathyroidism as evaluated by biochemical findings are very important, she said, and should be kept in mind when making treatment decisions (Underbjerg 2018). She presented two cases.

Case 1

The first patient treated with recombinant human parathyroid hormone (rhPTH(1-84)), trade name Natpar (EMA SmPC), in Austria had idiopathic hypoparathyroidism diagnosed at the age of 8 years. He was aged 50 years, working as a farmer and without typical hypocalcaemic symptoms. He did very well for a long time with standard therapy but eventually presented with serum calcium despite taking 1-4g of calcium carbonate and calcitriol 1.25 microg per day.

The rhPTH (1-84) 75 microg/day normalised calcium and phosphate levels within two months. Interestingly, he reported that he felt more emotionally stable, his mood was better and he was more physically active by this point. One year after initiation of treatment, laboratory values were stable. He took only a very small dose of calcitriol. He was unwilling to keep taking large doses of calcium after taking supplements for more than 40 years; this is a frequent complaint of patients.

Hypercalciuria

The gold standard measurement is 24-hour renal calcium excretion but in clinical practice, patients are reluctant to carry around the container. Whilst performing this test may be bothersome, it is still really important.

Case 2

The second patient was a 34-year-old woman with post-surgical hypoparathyroidism. She was started on rhPTH(1-84) 50 mcg in June 2018 for hypocalcaemia and for severe musculoskeletal symptoms (weakness and pain) which improved a lot on treatment. The dose was increased to 75 mcg 8 weeks before the time of speaking. The patient had severe hypercalciuria: her 24-hour urinary calcium was more than twice the reference range, putting her at risk for stones. Kidney ultrasound results were normal. She was also taking 0.5 microg calcitriol and a low dose of calcium. She was unable to tolerate thiazides.

Suggestions from the audience included measurement of the urinary sodium and checking other urinary stone risk factors such as oxalate and citrate. Dietary calcium and sodium could be reduced, although low-salt diets are really difficult and patients are generally not compliant.

Dr Amrein said she had stopped the patient's calcium and reduced her dose of rhPTH(1-84) again. The patient is young and she does have a very significant risk of renal disease.

The second part of the workshop was presented by Dr Symeon Tournis (Athens, Greece). He also presented two cases.

Case 3

The first case was a 59-year-old woman who had had post-surgical hypoparathyroidism diagnosed in 1996. In 2017 she had an aortic valve replacement due to aortic stenosis. She has chronic kidney disease stage 3 (eGFR 54.6 mL/min). In 2017 she was being treated with alfacalcidol 1.5 mcg twice daily and calcium carbonate 1 g twice daily. When she complained of symptoms of hypocalcaemia the dose of alfacalcidol was increased but both calcium and phosphate levels rose in response. We tried to keep the patient on a low phosphate diet, but it is difficult, he said. PTH therapy was commenced in order to keep the calcium higher because of the risk of CVD in patients having low calcium levels. Right now the patient is taking 50 mcg rhPTH(1-84), calcium carbonate 500 mg twice daily and she has serum calcium of 8.7 mg/dL and phosphate of 4.6 mg/dL.

The major reason for hyperphosphataemia in HypoPT is that the decline in PTH leads to a decline in phosphate excretion by the proximal tubule, and also treatment with calcitriol increases absorption of phosphate by the gut so the patient ends up having elevated phosphate levels.

Patients need to avoid dairy products and certain meats. Possible considerations include dividing the doses of calcium supplements during the day and reducing the dose of activated vitamin D. There is evidence that PTH treatment may help to maintain serum calcium levels and decrease phosphate levels. There is little evidence for the effectiveness of phosphate binders.

Case 4

This was a case of mild HypoPT in a pregnant patient. The patient was 32 years old and presented at 15 weeks of gestation. She had had post-surgical HypoPT since 2011. She was being treated with a low dose of alfacalcidol and twice daily 500 mg calcium but was not compliant with treatment. Six months later her calcium levels declined so the dose of alfacalcidol was increased and the calcium was kept the same. She had a normal delivery. For lactation, the dose of alfacalcidol was reduced and calcium measured frequently because reduced needs for calcium and activated vitamin D might be expected.

Comment: (from Bilezikian) during the last trimester the placenta becomes an endocrine organ, producing PTHrP. It may be possible to reduce the vitamin D and calcium doses because the placenta basically takes over. Some patients with HypoPT have said that the best time of their lives was when they were pregnant because they did not need so much calcium.

During pregnancy, total calcium levels slightly decrease due to haemodilution but ionised calcium remains the same. The PTH decreases early in pregnancy and then increases again. The adaptation is through an increase in calcium absorption.

During lactation, the major change is an increase in PTHrP which is produced by the breast. This increases bone remodelling and release of calcium from the bone.

Guidelines for the management of HypoPT during pregnancy (Bollerslev 2015; Wagner 2012; Kovacs 2016; Kahn 2019) indicate that there may be an increased requirement for vitamin D and calcium. Thiazide diuretics should be avoided. Ionised or albumin-corrected calcium should be monitored every 2 to 3 weeks throughout pregnancy and lactation. These are high-risk pregnancies whether the mother has high or low levels of blood calcium. There is a need for coordinated care between endocrinologist, obstetrician and paediatrician.

“Pregnancies are high risk in patients with chronic HypoPT”



Post-surgical HypoPT

Moderators: Professor Volker Fendrich (Germany) and Mr Tom Kurzawinski (UK)

Workshop 2 focused on post-surgical hypoparathyroidism and considered potential diagnostic and follow-up challenges and risk and prediction factors leading to chronic disease. The first speaker was Professor Volker Fendrich (Hamburg, Germany), who indicated it can be difficult to prevent complications after surgery.

Temporary hypoparathyroidism on the first day after surgery occurs in 10–15% of patients whereas permanent hypoparathyroidism rates are in the 1–3% range. About 11% of thyroidectomy specimens contained unintentionally removed parathyroid tissue in a study of specimens from 414 patients (Lee 1999).

Causes of post-surgical hypoparathyroidism

It is sometimes very difficult to identify the glands; they can be very small and very light and may be mistaken for lymph nodes, for fat or even for a thyroid nodule. In addition, due to the embryology of the parathyroid there are many different locations where they can seed (Randolph 2012).

Prevention of post-surgical hypoparathyroidism

The most important thing is to avoid unnecessary surgery. In Germany this is very common, partly because 1 in 2 people over the age of 45 years have a goitre or nodule, but actually carcinoma is very rare.

Sometimes it is necessary to operate, for example in those with huge goitres, but it may be possible to avoid total thyroidectomy. There is no indication for the prophylactic resection of a benign thyroid nodule. By doing only a hemithyroidectomy there is a zero percent incidence of post-surgical hypoparathyroidism. This of course needs a lot of discussion with endocrinologists because they have to follow up this normal gland, and patients have to be told that they may need further surgery.

Similarly, the American Thyroid Association 2015 management guidelines (Haugen 2016) recommend that papillary thyroid microcarcinomas confined to one lobe of the thyroid glands (implying node-negative tumours <1 cm) do not routinely require total thyroidectomy.

Autotransplantation

There is controversy about this procedure. One colleague says that if you do routine autotransplantation of at least one parathyroid gland during total thyroidectomy there will be no permanent post-surgical hypoparathyroidism at all (Zedenius 1999). Another paper from Germany (Trupka 2002)

supported these findings. Then there are totally opposite findings.

ICG fluorescence

Triponcz (2018) published a randomised trial of intraoperative parathyroid gland angiography which used indocyanine green (ICG) fluorescence to predict parathyroid function after thyroid surgery. If you put in ICG at the end of a thyroidectomy, the devascularised gland has no fluorescence but the well vascularised gland looks bright green. The authors concluded that ICG angiography reliably predicts the vascularisation of the parathyroid glands and obviates the need for post-operative measurement of calcium and PTH, and supplementation with calcium, in patients with at least one well-perfused parathyroid gland. Surprisingly, autofluorescence is very much restricted to the parathyroid gland.

Embryology
• Identification: normal parathyroid weight is only 35–40 mg and has a size of 5×3×1 mm
• Blood supply: same as the thyroid gland
• Inexperience of the surgeon

Fig 4. Causes of post-surgical hypoPT

The second talk by Mr Tom Kurzawinski (London, UK) addressed the issue of whether measuring ionised calcium at home and at the bedside in 30 seconds is possible and desirable. Patients with HypoPT develop symptoms whether their calcium supplementation is too high or too low. The only way to know whether they are receiving the right amount of calcium is to measure it. Guidelines (Bollerslev 2015) recommend “frequent” monitoring of the biochemical profile, but every 6 months is not frequent, he said. That thinking may be based on the difficulties of measurement.

Motivation for a change

It can be difficult to extract blood after surgery, especially in children, and there would be a big advantage if patients could measure their own calcium levels at home. Looking at other ways of measuring calcium could therefore be beneficial.

Choice of technology

After ruling out both complex and immature analysis methods such as spectrophotometry and spectroscopy, measuring ionised calcium was the best choice. It was established that ionised calcium can be used to monitor post-operative calcium levels. It was thought that intermittent and quantitative readouts would

be most helpful in making treatment decisions.

Once these choices had been made, the search began to find a device that could do this using venous and capillary blood, urine or saliva samples.

The answer was the LAQUA twin B-751 compact calcium ion meter made by the Japanese company Horiba; it is a tiny environmental measuring device the size of a pencil. Using ion-selective technology, it is very simple to use and measures the level of calcium in a single drop of various liquids, producing the result in less than one minute.

Testing the LAQUA twin B-751

It is a very complex process to test and recalibrate both the electronics and calibration fluids for a new device – especially when doing so for an orphan disease. This particular device only needs very small volumes of blood, opening up the interesting concept of using capillary blood rather than venous blood. But how could the device be successfully calibrated?

It transpired that Cornell University veterinary colleagues started to use the devices to measure samples from cows. As a consequence, many such devices were manufactured. After purchasing four devices, fluids were made up in our own department with various concentrations of calcium. The devices proved to offer good accuracy.

When peripheral venous blood samples of six healthy volunteers was compared to results obtained using the gold standard iSTAT in-vitro analysis platform, the ionised calcium measurements were found to only differ by +/- 4.5%.

Conclusions

Ionised calcium can be measured with this new device after thyroid and parathyroid surgery; the results with LAQUA look most promising; the device is portable, cost-effective and easy to handle.

A trial has been designed as a prospective pilot study of this particular device in 30 patients. The hypothesis is, changes in total and ionised calcium concentration in blood performed on gold standard platforms will be equivalent to changes in ionised calcium concentrations in different physiological compartments measured by LAQUA twin B-751.

If the device works it will rewrite the rules for patients with hypoparathyroidism because they can then measure calcium more frequently, similarly to the way in which diabetes patients measure their glucose.



The role of bone in normal mineral homeostasis and potential metabolic effects in HypoPT

Speaker: Professor John Bilezikian (USA)

Professor John Bilezikian (New York, USA) discussed the role of bone in normal mineral homeostasis and potential metabolic effects in hypoparathyroidism (HypoPT). Parathyroid hormone (PTH) has three major physiological functions: it regulates bone remodelling; it regulates serum calcium and phosphate; and it regulates 1,25 dihydroxy vitamin D levels.

Low bone turnover

HypoPT is a low bone turnover disease (Rubin 2011). In normal bone the osteoclasts stimulate the excavation of the bone microunit, which takes anywhere between 3–5 weeks. This is followed by replacement of bone first by type 1 collagen and then by mineralisation, which takes anywhere from 3 to 5 months. In HypoPT these processes are slowed down.

Bone quality suffers also. Bone turnover is low as assessed by reduced osteoid surface, reduced bone formation, reduced mineralised surface and reduced bone resorption rate when measured quantitatively on biopsy (Rubin 2008, Sikjaer 2011). However, circulating bone turnover markers are generally in the low-normal range, not frankly low. They therefore cannot reliably be used to define low turnover in HypoPT.

Structural features of bone

The Z score (a measure of bone mineral density [BMD] compared to age-related norms) shows above-average bone density in the lumbar spine, total hip and distal radius. This is a characteristic of HypoPT, with the exception being in post-menopausal women who develop HypoPT after they have lost bone density by virtue of oestrogen deficiency. Bone density typically correlates with duration of disease.

Both trabecular and cortical volumetric bone density have been investigated (Chen, 2003) using peripheral quantitative computed tomography (pQCT). In this study, women with HypoPT were compared to controls and also to subjects with hyperparathyroidism (PHPT). The HypoPT patients had an increase in trabecular vBMD at the distal radius and a sense of increase in cortical vBMD at the mid radius. Using microCT to look at trabecular architecture, cancellous bone volume is higher, trabecular thickness is greater and trabecular number is higher but trabecular separation is lower compared to controls.

Bone biopsies show the difference between HypoPT bone and bone in controls, with what appears to be greater thickness of cortical and

cancellous bone. The trabecular compartment also appears to be much more endowed. The trabecular bone in HypoPT patients on microCT images is so solid that it does not look like trabecular bone at all (Rubin 2018). It actually can resemble cortical bone.

An interesting theory that needs to be investigated is whether PTH is a regulator of compartmentalisation of bone, such that in hyperparathyroidism, we see the opposite; a disproportionate amount of trabecular bone, and less cortical bone. In HypoPT the lack of PTH may be associated, thus with the corticalisation of trabecular bone.

New imaging modalities

A newer technology, high resolution peripheral quantitative CT, is a type of non-invasive high-resolution imaging of the radius and the tibia. It allows measurement of various cortical and trabecular parameters. Dr Bilezikian referred to findings in the radius and tibia of women with HypoPT compared with the control population (Cusano 2016). In patients, there is increased cortical density, total density at the radius and trabecular number at the tibia. There is also decreased cortical porosity and decreased cortical and trabecular thickness at the tibia. Despite the abnormalities in these parameters, bone strength does not seem to be affected. This is a biomechanical discussion of stiffness versus toughness: increased stiffness may indicate stronger bone but not necessarily better bone.

Bone properties in HypoPT are summarised in the table.

Increased cancellous bone volume¹
• Increased trabecular number and thickness ¹
• > Plate-like structure ²
Decreased cortical thickness¹
Decreased remodelling rate¹
Increased mineralisation¹ and collagen maturity³
Fracture data are limited⁴
Fig 5. Summary of bone properties in hypoPT
(Adapted from 1. Casano N, 2016, 2. Rubin MR, 2010, 3. Paschalis EP, unpublished data; 4. Bilezikian J, opinion)

Fracture data

One might infer that because bone mineral density is above average, fracture risk should be reduced. Under normal circumstances that point should be relevant. But bone turnover is markedly reduced thus bone is hypermature

and maybe brittle; this bone might resist stress to a certain point but then shatter like glass. The balance between stiffness and toughness should favour bone that resists biomechanical stress up to a point but when these forces are exceeded it would be much more problematic.

The discussion is hampered by a lack of comprehensive fracture data despite some study findings. For example, Underbjerg (2014) showed that post-surgical and non-surgical HypoPT patients had no difference in overall fracture risk compared to the control population although there were specific subgroups with an increased or decreased fracture risk. There is a need to pool collective international experience, so that we have better epidemiological data regarding fracture risk in HypoPT.

Use of rhPTH(1-84)

With rhPTH(1-84) therapy, the skeleton “wakes up”. Trabecular width is reduced, cortical width increases, BMD distribution falls transiently, trabecular number increases and, interestingly, cortical porosity goes up. Four-year data (Cusano 2013) show that there is a burst of activity both with regard to bone formation and bone resorption turnover markers but then after 4 years these levels settle down to levels that are higher than the patient’s baseline, but are now within the standard and more normal distribution of euparathyroid subjects. It has now been shown in more recent 6-year data (Rubin 2016) that the bone formation markers P1NP and s-CTX are still much higher at 6 years than they were at baseline.

Four years of continuous rhPTH(1-84) treatment is associated with increases in lumbar spine BMD (Cusano 2013). The hip regions do not change very much. BMD falls at the distal third of the radius. The same pattern is observed at six years. In the most recent study (Tay 2019), the first 8-year data in this disease shows the lumbar spine and hip region BMDs remain above baseline and that of the distal radius continues to fall.

Summary

The bone in HypoPT is very abnormal in terms of its structure and dynamics. The relationship between these abnormalities and bone strength per se as well as in fracture incidence is uncertain. With rhPTH (1-84) skeletal dynamics are improved; BMD and microstructural elements respond in the ways expected but how this therapy affects fracture risk is unknown.



Potential tools helping the evaluation of cognitive symptoms in HypoPT and their pertinence to QoL measurements

Speaker: Professor Leif Østergaard (Denmark)

Dr Leif Østergaard (Aarhus, Denmark) spoke about cognitive symptoms in HypoPT and tools to assess their causes, severity and impact on quality of life. He also spoke about the possibility of seeing brain changes on imaging in these patients.

Quality of life

Various questionnaires can be used to address patients' quality of life. The short form SF-36 health survey is a very common one which scores between 1 and 100. Domains specifically related to the brain are vitality and mental health. Patients fill out the answers themselves without requiring a psychologist. An even faster index is the WHO-5 Well-Being index, and that is also widely reported.

Astor (2016) showed that surgical and non-surgical HypoPT and pseudo-hypoparathyroidism patients score significantly lower on the vitality and mental health domains of the SF-36 compared to normal subjects in the same population. For instance, vitality scores were 42.2 for HypoPT compared to 60.0 for controls. They also administered the Hospital Anxiety and Depression scale (HADS) where a higher score is suggestive of anxiety and depression, and found quite significant changes in score. For example, the anxiety score in HypoPT patients was 6.5 compared to 4.2 in controls.

The study concluded that there were 26% with clinical depression and 38% with clinical anxiety among a total number of 283 patients. These patients are severely affected in terms of their mental health. This is consistent with changes from another study (Underbjerg, 2014), which showed higher rates of depression or bipolar disorder in patients with post-surgical HypoPT.

Brain fog

This is seen, for instance, in cancer patients who receive radiation therapy to the head, in patients who get chemotherapy and also in multiple sclerosis patients with multiple lesions. Aspects include impaired ability to focus and concentrate, forgetfulness and lack of mental clarity. It is very unspecific and is difficult to measure. However, symptoms seem to be related to PTH levels. There are anecdotal reports of patients improving on PTH and there is a study showing that the quality of life domain scores improve with PTH replacement.

Neuroradiological findings

Are there brain changes that might explain this? It turns out that 75% of idiopathic HypoPT patients have basal ganglia ossifications, which is otherwise a very rare condition. The very first images taken before World War II showed a bright area, essentially calcium present in the basal ganglia of these patients. Interestingly, at the same time they reported in autopsy material that the capillaries in the brain were highly abnormal, there were deposits in and around the capillaries in these brains. These ectopic calcifications are now known to be initiated by pericytes (Collett 2005).

Pericytes

These small cells, which are embedded in the basement membranes around capillaries, have numerous functions. For example, in the presence of an infection the pericytes interact with the basement membrane and endothelial cells to thin out the basement membrane and retract the coverings of the capillaries to allow immune cells to enter the tissue and combat infection. They are critical for formation of new vessels and maintenance of their integrity (Armulik 2005). They are mesenchymal stem cells which means that they may be osteogenic, chondrogenic, adipogenic, fibrogenic or myogenic.

Specifically for the brain, the pericytes control capillary diameter, cerebral blood flow and the blood-brain barrier and they also express PTH1 receptors in the brain cortex. They constrict and die when exposed to amyloid-beta or oxidative stress.

What is the significance of changes in pericytes and capillary function? It was previously thought that oxygenation of any tissue is just a matter of having sufficient blood flow with the arterioles controlling cerebral blood flow and oxygen supply. But as blood goes through the capillary bed it only has less than a second to equilibrate with the tissues around it: the diffusion exchange with the tissue is very, very short. If capillary flow is very homogenous then things will work well but when that is no longer the case then deficits in capillary function may be observed (Vokes 2019). If some of these connections become slightly constricted and others become more open then blood can start to shunt through the microcirculation and essentially come to the venous side without having exchanged oxygen with tissue. It turns out that it is possible to have tissue hypoxia without ischaemia.

Assessing the microcirculation

Dr Østergaard described work which sought to discover whether there is anything wrong with the distribution of flow in capillaries. It is possible to inject a contrast agent into the brain, to take MRI images of cerebral blood flow and to measure the mean transit time (MTT) of the blood through the microvasculature. It is also possible to measure the heterogeneity of flow, capillary transit time heterogeneity (CTH). That gives a handle on the extent to which blood is shunted through the microcirculation.

He showed images from Alzheimer's disease patients and age-matched controls without Alzheimer's. The images showed disturbed capillary flow in the patients, and this is something that could not be seen before use of this new technique.

Since there seem to be similarities between patients with mild cognitive impairment and those with HypoPT, he went on to investigate whether there was disturbed capillary flow in the brains of patients with HypoPT. What was striking was the presence of bright areas of blood-brain barrier breakdown. The pericytes are an important part of the blood-brain barrier so these findings are consistent with the notion that there could be something wrong with pericyte function in these patients.

Control capillary diameter (contractile)

Control CBF

Control blood-brain barrier

Express PTH1 receptors

Constrict when exposed to:

- Amyloid- β (Alzheimer's disease)
- Oxidative stress⁷

Fig 6. Brain pericytes (Østergaard)

Summary

Most quality of life tools are self-administered. They address general wellbeing and also quantify both motor function and also mood and neuropsychological functioning. Quality of life is clearly reduced across all domains in HypoPT patients. HypoPT is associated with anxiety, depression, brain fog and basal ganglia calcifications. In these patients there is also blood-brain barrier dysfunction, and it may reflect pericyte dysfunction.



When is the HypoPT patient not well controlled? Guidance and clinical experience

Speaker: Dr Peter Kamenický (France)

Session 2 focused on those patients with HypoPT who are not well controlled. The first speaker was Dr Peter Kamenický (Paris, France). HypoPT is a deficiency of parathyroid hormone (PTH): in adult patients 75% of cases are iatrogenic, caused by injury to parathyroid tissue during neck surgery.

Pathophysiology of HypoPT

Patients who lack PTH will suffer from various consequences. First, there is a lack of calcitriol production, which will decrease intestinal calcium and phosphate absorption. Second, there is a lack at the kidney level of the phosphaturic action of PTH and an increase in urinary calcium excretion. And third, there is decreased bone remodelling. Conventional treatment with calcium supplements and activated vitamin D derivatives stimulates intestinal calcium absorption but does not act at the kidney level and does not improve the decreased bone remodelling.

Inadequate clinical and biochemical control

Patients need adequate doses of activated vitamin D and calcium supplementation in order not to have symptoms of hypocalcaemia such as paraesthesiae or cramps. Giving too much calcium can lead to hypercalcaemia and hypercalciuria and these may result in complications such as nephrocalcinosis, nephrolithiasis or brain calcifications.

There is an alternative to this treatment, which is PTH replacement therapy with human recombinant PTH (1-84), which is approved in the US and conditionally approved in Europe. This approach compensates for the whole pathophysiology of the disease.

Considering the literature that advises clinicians who are not adequately controlled and are good candidates for PTH replacement therapy, there are some important sources: the ESE 2015 guidelines (Bollerslev 2015), the first international conference on the management of HypoPT (Brandi 2016, Bilezikian 2016), the American Thyroid Association statement on postoperative HypoPT (Orloff 2018) and the new Canadian and international consensus on the management of HypoPT (Khan 2019). The problem is that these recommendations are mainly based on expert opinions and small studies.

Treatment goals

The first goal in the ESE 2015 guidelines is to maintain the serum calcium level, either albumin-adjusted total calcium or ionised calcium, in the lower part of the reference range or a little bit below the lower limit of the reference range as a target range for patients. The problem is that it is not possible to know what the optimal calcium level is for an individual patient. Sometimes the biochemical parameters look good but the patient complains of neuromuscular symptoms, and eventually cardiovascular symptoms and others.

The second important point is calciuria. It is recommended to try to keep the 24-hour urinary calcium excretion in the sex-specific reference range. With a hypercalciuric patient clinicians should look at two parameters: the sodium intake is an easy parameter to control – some patients are hypercalciuric because they eat too much salt. There is a clear linear correlation between salt intake and calciuria. The second one is protein intake, which can be easily measured and appreciated from the urine, looking at the urea. There is also a relation between protein intake, people who eat too much meat, and calciuria. So these two parameters can be addressed.

Imaging of the kidney should be performed to detect renal stones and nephrocalcinosis. Some perform ultrasound; Dr Kamenický said that he performed a CT scan at least once because it is better for seeing calcification in kidney tissue but there is no real consensus on this.

The next important point is to keep serum phosphate levels in the normal range and the calcium-phosphate product below $4.4 \text{ mmol}^2/\text{L}^2$. High phosphate and a high calcium-phosphate product result in increased risk of extraskeletal calcifications in kidney, eye and brain.

Further steps include keeping serum magnesium levels within the normal range; personalising treatment; and focusing on the wellbeing and overall quality of life of the patient when implementing therapeutic efforts. The final recommendation is to educate patients on the symptoms of hypo and hypercalcaemia as well as the co-morbidities.

Control

Characteristics of patients who are considered not adequately controlled on standard therapy are summarised in Brandi (2016). First, patients whose serum calcium is inadequately controlled, maybe due to intercurrent illness, compliance or absorption issues. Second, patients who need excessive doses of oral calcium or vitamin D derivatives, for example more than 3 microg of the analogue per day. Third, patients with persistent hypercalciuria, nephrocalcinosis, renal stones or decreased renal function. Fourth, patients with hyperphosphataemia or increased CPP. Fifth, patients with gastrointestinal tract abnormalities associated with malabsorption or after bariatric surgery. Finally, and more difficult to assess, reduced quality of life.

There is clearly an effort in the expert community to define the profile of patients who are not adequately controlled. There have been 3 Delphi panels, and they have defined four groups of patients according to whether they have normal or abnormal biochemistry and whether they feel well or unwell.

Definition of good HypoPT control

This is summarised in figure 7.

- Normal biochemical criteria (easily measurable)
- Low complications and comorbidities
- High Quality of Life (QoL)
- Good correlation between biochemistry and perceived wellness?

Areas of uncertainty

- Better identification of patients with not adequately controlled hypoPT on standard treatment to select candidates for recombinant human parathyroid hormone (rhPTH(1-84)) therapy
- Delphi consensus panels in UK and Sweden

Fig 7. Definition of good HypoPT control
(Speaker view)

A patient with normal biochemistry and no symptoms can reasonably be described as well controlled. A patient with abnormal biochemistry and impaired quality of life, symptomatic and with co-morbidities is a good candidate for change of therapy to PTH replacement treatment. The real problem is the patients in the grey area of uncertainty where defining the best treatment is difficult; there is more work to be done to define the profile of these patients.



Patient cases with multisystem co-morbidities: Is there a common thread?

Moderators: Dr Sigridur Björnsdóttir (Sweden) and Professor Salvatore Minisola (Italy)

Workshop 3 considered patient cases with multisystem co-morbidities, asking whether there was a common thread. The first speaker was Dr Sigridur Björnsdóttir from Stockholm, Sweden.

Case 1

A 43-year-old woman with post-surgical HypoPT was referred for a total thyroidectomy in 2013 for papillary thyroid cancer. She had symptoms of fatigue, muscle spasm, pain, paraesthesiae and brain fog.

One year after surgery, she was admitted to hospital with hypercalcaemia. She had high ionised calcium and the serum phosphate was at the upper end of the reference range. She had pain at the left side of the back and haematuria. A CT scan of the urinary tract showed a 1 mm stone in the left kidney. The GFR and creatinine fluctuated, and she described passing gravel occasionally. Since then she has had a few more stones and frequent urinary tract infections.

Kidney stones and renal insufficiency

A study from Denmark (Underbjerg 2013) showed that there is a 6-fold increased risk of renal insufficiency for non-surgical HypoPT and a 3-fold increase in post-surgical HypoPT patients. For post-surgical HypoPT there was a 4-fold increased risk of kidney stones but it was not significant for non-surgical patients.

The patient's current treatment was alfacalcidol three tablets twice a day, calcium carbonate 500mg and vitamin D3 800 units, magnesium 250mg, thyroxine 125 or 150 microg, and a low dose of a thiazide diuretic. She insisted she was compliant with her treatment.

There are not a lot of treatment options in Sweden, with only one patient currently on rhPTH (1-84). So the patient started using teriparatide PTH(1-34)* in May 2019, but after three weeks she became worse and stopped taking the medication.

If this patient did not tolerate teriparatide PTH(1-34)*, perhaps she might benefit from rhPTH (1-84); it might reduce the urinary calcium level and enable calcium supplements to be reduced. The patient is similar to others included in the RACE study (Mannstadt 2019), who took time to reduce their urinary calcium. This is a matter of concern because this patient has already had plenty of kidney stones, and it took almost a year for most women in that study to successfully reach the end goal.

The second part of the workshop was presented by Professor Salvatore Minisola (Rome, Italy).

Case 2

A 37-year-old female presented to the emergency department complaining of weakness, dyspnoea on exertion, chest heaviness and palpitations. The patient's history included HypoPT that complicated a total thyroidectomy performed 5 years before because of goitre. She was on therapy with 1,25 (OH)₂ vitamin D and calcium salts, with biochemical values within the normal range. However, in the last week she had had acute diarrhoea which had not resolved, so perhaps these drugs were not being well absorbed as a consequence.

Chest auscultation revealed bilateral basal crepitations. Cardiac enzymes were within the normal range. Echocardiography showed global left ventricular hypokinesia, with an LVEF of 32%. The patient was initially treated with diuretics, beta blockers and an ACE inhibitor. Her value of serum calcium was 7.0 mg/dL but in the acute phase of diarrhoea it may have been even lower. Phosphate levels were high at 5.0 mg/dL. She was initially treated with calcium gluconate intravenously followed by a continuous infusion. After 3 days, when the situation was normalised, treatment with 1,25 (OH)₂ vitamin D and calcium salts was restarted.

The patient was discharged from hospital, on therapy with diuretics, beta blockers and ACE inhibitors that were gradually tapered. After 4 months she was asymptomatic. Echocardiography performed 1 year later showed an improved LVEF of 52%.

Hypocalcaemia and cardiomyopathy

A paper published in the JCEM (Bansal 2014) described two cases of dilated cardiomyopathy in patients with hypocalcaemia. The first one was a patient in some ways similar to the previous case reported. The second one was a baby who presented in cardiogenic shock. The calcium in this case was very low at 4.5 mg/dL, serum phosphate at 11.9 mg/dL (in infants serum phosphate levels are normally much higher than those in adults), 1,25 (OH)₂ vitamin D was very low at 8.9 ng/mL and there was also secondary hyperparathyroidism. In this case supplementation with calcium and calcitriol resulted in complete clinical and haemodynamic recovery.

As regards serum calcium levels in patients with heart failure, Jensen (Jensen, 2019) described a large database of about 5,000 patients with heart failure. Mortality in those with both high and low serum values of calcium was increased compared to that in patients with normal serum calcium levels of 1.18-1.32 mmol/L.

Case 3

A young woman of 23 presented to the emergency department complaining of palpitations and breathlessness. She reported these episodes many times during the day for a couple of months. She had undergone partial thyroidectomy four years before for a multinodular goitre.

Her resting pulse was 64 bpm and blood pressure 120/70 mmHg. Biochemistry showed low serum calcium, high phosphate, PTH that was abnormally low in respect to the calcium values, and no significant changes in thyroid hormone or magnesium levels. An ECG showed a possible junctional rhythm but more importantly a prolonged corrected QT interval of 500ms. This prolonged QT interval implies a number of electrophysiological derangements that can be life-threatening. 24-hour Holter monitoring revealed that there were many ventricular premature beats and a single episode of atrial tachyarrhythmia. The patient was treated with calcium and vitamin D therapy. After two months her biochemical parameters returned to normal and on 24-hour Holter monitoring no abnormalities were recorded.

The calcium ion is important not only for muscle contraction but for cardiac conduction. Low calcium values imply a number of abnormalities.

Dr Minisola's main message from these two cases was to pay attention not only to bone, brain and kidney but also to cardiac abnormalities. One of the main causes of long QT interval is electrolyte disturbances, and the first of these is low serum calcium.

“Pay attention to cardiac abnormalities in HypoPT”

* PTH 1-34 is used off-label in HypoPT.



Patient cases with persistent neurocognitive symptoms and impaired quality of life

Moderators: Professor Heide Siggelkow (Germany) and Dr Tanja Sikjaer (Denmark)

Workshop 4 considered the issue of patient cases with persistent neurocognitive symptoms and impaired quality of life (QoL). The first speaker was Dr Heide Siggelkow from Göttingen, Germany. The cognitive symptoms in chronic HypoPT are described as brain fog and inability to concentrate. Emotional difficulties may include depression and anxiety. It is currently not known whether the disease, the biochemistry, the medication or something else results in these symptoms.

The complaints of HypoPT patients are serious. QoL in patients with non-surgical HypoPT was compared to patients with depression, heart disease and diabetes (Underbjerg 2018). Patients with HypoPT had worse physical and social functioning than those with depression; they had worse physical functioning, mental health and social functioning than those with heart disease; and they were worse affected in all these areas than patients with diabetes.

New measures of QoL

There are three published tools now to measure quality of life. They are the HypoPT symptom diary (Coles 2019), the hypoparathyroidism patient experience scale-symptom (Brod 2019) and a specific questionnaire for HypoPT patients (HPQ, Wilde 2019).

In relation to the symptom diary, Dr Siggelkow presented her personal analysis (Siggelkow, poster ECE 2018) of an anonymous patient survey of patients with chronic HypoPT who were not adequately controlled from their own perception. The burden of illness was measured according to the severity of symptoms as assessed by the hypoparathyroidism symptom diary. The survey showed the impact of the disease on their quality of daily life—the impact on sleep, ability to exercise, ability to work and on family relationships. A huge number of patients have moderate or severe problems with daily life.

The HPQ 28

This disease-specific questionnaire has been developed over the past 5 years. By taking the positive results compared to the normative control from previous questionnaires, a new questionnaire of 40 questions has been created. This has then been used prospectively for three groups—the post-surgical group, a group just operated on for thyroid disease (without HypoPT) and a group with primary hyperparathyroidism (PHPT).

From these groups, ten domains were identified, described as pain and cramps, neurovegetative symptoms, vitality, depression and anxiety, gastrointestinal symptoms, tingling, heat conditions, troubled memory and a PHQ-2 depression scale. Some of the items were clearly significantly different from the two control groups. Analysing what influences these complaints, the calcium-phosphate product correlated with many of them and the serum calcium was correlated with neurovegetative symptoms.

In conclusion, HypoPT is a severe disease associated with a number of complications, increased mortality and reduced quality of life. It is now possible to use three different measures, which will need to be validated further in other populations and in longitudinal studies.

The second speaker was Dr Tanja Sikjaer from Aarhus, Denmark. What PTH does in the kidneys and bones is relatively well known but what it does in the brain is more uncertain.

There are two PTH receptors expressed in the brain: the PTH/PTHrP (PTH-related protein) receptor and the PTH2 receptor, which is found mostly in the brain and in the pancreas (Usdin 1995).

HypoPT and cognitive impairment

There are few studies but plenty of case reports. The first study Dr Sikjaer described (Kowdley 1999) compared 11 patients with HypoPT and gender, age- and education-matched controls. It found cognitive impairment in 64% of the patients, but there was only a weak positive relationship between cognitive impairment and calcifications.

In another study (Aggarwal 2013), comparing 62 patients with idiopathic HypoPT with 70 controls, found that 32.3% of patients had neuropsychological dysfunction compared with 5.7% of controls. There was a correlation between neuropsychological dysfunction and duration of illness, female gender, plasma calcium and calcium-phosphate product but not with intracranial calcifications.

MRI project

A new MRI project is being set up to find out whether this impaired quality of life and mild cognitive impairment in patients with HypoPT can be measured by MRI scans and whether it could be explained by disturbed capillary flow patterns in the brain. The study will include 25 patients with post-surgical HypoPT, 25

healthy controls, 15 patients with non-surgical HypoPT and 15 patients with pseudoHypoPT. All the patients will undergo a great deal of neuropsychological testing before the MRI scans.

Dr Sikjaer described two of the patients included in the study; the first being a 42-year-old woman who developed post-surgical hypothyroidism and HypoPT 20 years ago. The patient has been very difficult to control, and has been to the emergency department for both hypercalcaemia and hypocalcaemia with a prolonged QTc interval. She has spent quite a lot of time with her ionised calcium outside the reference range and has unmeasurable levels of PTH.

Her physical symptoms include many episodes of paraesthesiae, extreme tiredness, reduced memory and concentration difficulties. Her MRI scans show no calcifications and no white matter lesions but a large ventricular system.

The second case was a 49-year-old woman who also developed post-surgical hypothyroidism and HypoPT after total thyroidectomy. She is well controlled on alfacalcidol and calcium but she nevertheless has a lot of symptoms. Her mental and cognitive symptoms are reduced memory, mental tiredness, difficulty concentrating and slow thinking. Her MRI scans also show no calcifications and no white matter lesions.

Using MRI scans to compare the first case, the second case and a healthy control using relative capillary transit time heterogeneity (RTH), capillary transit time heterogeneity (CTH) and mean transit time (MTT), there are differences between the cases and control. There are more frontal changes in the patients whereas it looks more normal elsewhere. The conclusions from the workshop are summarised in figure 8.

- There is little data on cognitive function in HypoPT
- Potential causes of impairment:
 - Intracranial calcification
 - Insufficient or missing PTH
 - Changes in capillary flow patterns in the brain (maybe through pericytes)
 - Fluctuations in calcium levels
 - Chronic low calcium levels, just below or in the lower end of the normal reference range

Fig 8. Workshop 4 conclusions



Summary expert perspectives from Session 1 and 2

Chair: Professor Neil Gittoes (USA)

Faculty panel: Professor Karin Amrein (Austria), Dr Sigrídur Björnsdóttir (Sweden), Professor Volker Fendrich (Germany), Dr Peter Kamenický (France), Professor Salvatore Minisola (Italy), Professor Heide Siggelkow (Germany), Dr Tanja Sikjaer (Denmark) and Dr Symeon Tournis (Greece)

Multiple risk factor assessment

The moderator for the discussion of all sessions from the first day was Professor Neil Gittoes (UK).

He began by asking how far away we are from establishing a multifactorial risk assessment tool analogous to Fracture Risk Assessment Tool (FRAX®), which will allow the incorporation of variables to define what an inadequately controlled HypoPT patient is.

Kamenický: it would be attractive to have some scoring system to tell us whether to put the patient onto PTH replacement therapy. We are dealing with a rare disease here, not osteoporosis, so it would be more complicated to get this kind of scoring system but people are working on the registries and gathering more and more data.

Clarke: it is encouraging that various studies are gathering a dataset that can be analysed to see what the most significant risk factors are.

Audience: we are endocrinologists, and we know that treating patients with the hormone that is lacking is better than any other treatment. If PTH were available for everybody we would treat all our patients with this drug. Second, it is difficult to differentiate whether the reason for their low quality of life is low thyroid levels or hypoparathyroidism.

Minisola: in general the utilisation of rhPTH(1-84) is better than any previous kind of therapy. The problem is how therapy can be allowed to patients. What is the basis apart from theoretical deterioration in quality of life in order to prescribe rhPTH(1-84)? The regulatory authorities will want to know.

Quality of life measures

Siggelkow: we know now that quality of life is reduced. It is not something weird: you get clear numbers if you use specific tools to measure it in HypoPT. These numbers can be used to decide treatment.

Kamenický: nowadays we are on a scale of different shades of grey but some indications are very clear, for example a patient after bariatric surgery with malabsorption who takes a high dose of alfacalcidol. This is obviously a very good indication for PTH replacement and I think any health authority would recognise this. Then we have other groups of patients where we need to measure for example quality of life, muscle function and other indicators to

show that this treatment is going to improve something.

Fendrich: perhaps we should measure quality of life before surgery and then see how it has changed. This could be another control arm.

Sikjaer: we do not have the studies that show that PTH treatment actually improves quality of life. Of course we all have patients who we have treated and who seem to get better but we do not have the data that show that it is the hormone itself that causes the improvement.

Physiological or not

Amrein: the current once-daily PTH application still is completely unphysiological for a hormone that in vivo has a half-life of minutes so it is well comparable to diabetes care 50 or 60 years ago.

Gittoes: so do we think we are stifling the potential of our observations by undertreating.

Amrein: Yes, of course. If you compare this with other drugs it is completely logical that if you give antihypertensive medication once a month it would not help.

Bilezikian: the bulk of data would argue that the majority of patients would meet guidelines for treatment with rhPTH(1-84). There will be some patients who can do very well without it but I think that is going to be the minority.

Prevention of HypoPT

Bollerslev: how do we prevent chronic HypoPT in the surgical department?

Fendrich: in my opinion as a surgeon the most important thing is to avoid unnecessary surgery because there are experienced colleagues from all over the world doing their best but the numbers of post-surgical HypoPT are not down to zero.

Kurzawinski: the surgical complications are a huge issue and are grossly under-reported.

Gittoes: my thoughts are that the quality of life issue is a big threshold in terms of access to the drug. If more people have access to the drug for longer periods it will give us more of an idea about how the drug changes the natural history.

Kidney function

Tournis: the treatment improves levels of phosphate, calcium-phosphate product, reduces calcium supplementation and urinary calcium levels, but all these are indirect



HypoPT affects quality of life (©Shutterstock)

measures. We need more data about the natural history of kidney function during treatment with PTH versus conventional treatment.

Kamenický: we clearly also need data on long-term safety in terms of kidney and bone health, for example in patients who are replaced with PTH 1-34* and rhPTH 1-84.

Measuring calcium excretion

Gittoes: in all the guidelines we talk about 24-hour urinary calcium excretion but we only achieve it in about 20-30% of patients annually. If we do mean this, we should be pushing hard to get this done. There should be professional pride in doing it and we should be interpreting it.

Kamenický: we do not have data that urinary excretion is impacting on mortality, and probably we will never have this kind of data, but I think that we should be more demanding on having this measurement.

Magnesium supplementation

Audience: patients dislike taking magnesium. How hard should we be chasing a marginally reduced serum magnesium?

Tournis: I am not aware of any data that really tested in HypoPT whether treatment with magnesium led to an improvement in the symptoms.

Clarke: what I hear from patients is that if I just give them calcium alone, they tend to become constipated. Many of those patients take magnesium because it makes their constipation less troublesome. I think there are practical reasons to consider low-dose magnesium at least 250-400 mg once or twice a day.

* PTH 1-34 is used off-label in HypoPT.



Current guidelines and anticipated updates: Key learnings and challenges from clinical practice

Speaker: Professor Jens Bollerslev (Norway)

Professor Jens Bollerslev (Oslo, Norway) gave the keynote presentation on current guidelines and anticipated updates, summarising what has been learned over the past five years.

There are guidelines at different levels in clinical practice. Regarding those from international collaborations and societies, there should be solid evidence behind recommendations or they should declare that no solid evidence exists.

Increased interest in HypoPT

There has clearly been an increase in interest in the management of HypoPT over the last 20 years, and especially over the last decade, but there are few random clinical trials (RCTs) to draw on since publication of the European clinical guideline in May 2015 (Bollerslev 2015). Consequently, a review was published in the NEJM just a few months ago (Gafni 2019), and the recommendations in the 2019 review are generally consistent with the guidelines that were written 5 years ago.

Time to update

In his talk, Professor Bollerslev outlined the case for it being time to update the guideline, as the number of publications and new knowledge gained since 2015, had raised a lot of new attention on the subject.

The place of substitution therapy

At the time the guideline was written, it was clearly stated that putting substitution therapy as the primary treatment option was not a consideration. Subsequently, it is now clear there are some indications for considering the use of rhPTH(1-84) as part of the treatment algorithm (Brandt 2016). They include inadequate control of the serum calcium concentration, excessive doses of oral calcium/vitamin D medications, hypercalciuria, hyperphosphataemia and reduced quality of life.

Adherence to guidelines

What is the degree of adherence to the ESE guidelines? Meola (2018) looked at adherence to ESE guidelines and the risk of renal complications. They had 90 patients with HypoPT and they had four targets from the guideline flow chart. Two thirds of patients did not meet the criteria on conventional therapy.

Most patients actually do have a lot of symptoms in their daily life. One publication (Astor 2016) on epidemiology and health-related quality of life in Norway has been published since the guidelines came out five

years ago. The striking finding here is the amount of reduction in quality of life compared with normative data. Even comparing them with Addison's disease patients, it was clear that patients with HypoPT have a more significant reduction in quality of life. This is especially low among post-surgical patients and among women. This aspect of HypoPT has socioeconomic effects for society; 40% of the patients were on social benefits at the time of the investigation (compared with 10% of the general population).

Quality of life and recent replacement studies

In an open study (the extension from the REPLACE study), patients were randomised to rhPTH(1-84) or placebo, where the primary endpoint was quality of life based on SF-36 (Vokes 2018). There was overall no treatment effect but there was a positive within-group effect and a positive effect in subgroup analysis.

Additionally, work from the Columbia group on quality of life (Tabacco 2019), the SF-36 findings of twenty patients receiving hormone replacement therapy treatment over 8 years were compared with normative data at baseline. Compared with the reference population, those with chronic HypoPT had reduced quality of life in the eight domains at baseline and then improvement in many of the domains with long-term substitution therapy.

The data we have so far are based mostly on generic questionnaires, especially SF-36, and these several small open studies indicate positive effects of replacement therapy on quality of life. The good news is that more randomised trials based on disease-specific questionnaires are on the way.

Safety

Chronic HypoPT is more than just low calcium and inappropriate PTH levels. Calcium is very tightly regulated in normal physiology but it fluctuates in HypoPT. We are entering an era where we may be able to measure a patient's calcium at the bedside many times a day, and this will of course be beneficial to patients. Although calcium is low in HypoPT the phosphate is high and the calcium-phosphate product, a risk factor for calcifications, should be kept low. Urinary calcium excretion is high and should be kept within age- and sex-matched normal values.

Co-morbidities

The co-morbidities are more severe in idiopathic than in post-surgical HypoPT but overall mortality is not changed. The most recent study on complications (Underbjerg 2018) based on 431 patients concluded that high phosphate levels compared with low phosphate levels in this group were associated with increased mortality and risk of any infection. So phosphate seems to be a determinant for long-term complications. A high CPP was associated with increased mortality and risk of renal disease. Lower than normal calcium levels were associated with increased risk of cardiovascular disease. Mortality and risk of complications increased with the number of hypercalcaemic episodes and disease duration.

Moderate evidence that most treatment regimens are capable of reaching normocalcaemia

No evidence for optimal treatment (drug choice, calcium target) with respect to:

- Mortality
- CV disease
- Long-term renal function/nephrolithiasis
- Disability/sick leave
- Seizures/tetany/severe hypocalcaemia

Fig 9. Evidence concerning HypoPT treatments

Conclusions

There have been no new RCTs in the last 5 years but we do have data from long-term open studies. These too are important because they provide a lot of knowledge and experience and are hypothesis-generating. The quality of life data that we have so far are based on generic questionnaires: they demonstrate repeatedly that chronic HypoPT in adults is a burdensome disease. The complications risk is elevated and is related to biochemistry.

Professor Bollerslev reiterated that he felt the guidelines should be updated. Clinicians should focus on their experiences so far with the different kinds of treatments, the burden of disease as experienced by the patients, quality of life (which is of importance for society), and should try to identify the risk factors for complications and mortality.



Parathyroid hormone as a direct management option in patients with chronic HypoPT

Speaker: Professor Bart L. Clarke (USA)

Professor Bart L. Clarke (Rochester, USA) gave a plenary presentation on parathyroid hormone (PTH) as a direct management option. He reviewed the current clinical use of rhPTH(1-84) in chronic HypoPT and discussed the clinical challenges in managing the patients who are treated with this drug.

Early experience

The concept of PTH therapy dates back to 1929, when Fuller Albright treated a 14-year-old boy with post-surgical hypoparathyroidism over 4 days with injectable PTH extract. Therapeutic effects on serum and urinary calcium and phosphorus were observed.

Many years later, Winer (1996) published the effects of PTH (1-34) on serum and urine calcium. She compared the changes in urine calcium with calcitriol and then PTH in adults. This is a two-hormone disorder and each of these hormones has an effect.

The REPLACE trial

This phase III randomised controlled multinational trial (Mannstadt 2013) recruited 134 patients, who were randomised 2:1 to drug versus placebo. The treatment duration was 24 weeks.

The aim of the trial was to find out whether rhPTH(1-84) reduces the need for calcium and vitamin D supplementation in patients with HypoPT. Over the 24 weeks the primary outcome was the triple endpoint. To be considered a responder, patients had to have a greater than 50% reduction in calcium and the active vitamin D that was being used while maintaining serum calcium above baseline and below the upper limit of normal. At the end of the 24 weeks, 53% of patients on the drug achieved that primary outcome versus only 2% in the placebo group. Adverse events were similar in the two groups. The conclusion of that study was that this drug was efficacious for the purpose designed and well tolerated.

“PTH therapy offers options for controlling serum calcium more effectively”

Efficacy endpoints and safety analysis

There were a number of secondary endpoints, including the percentage of patients who achieved independence from supplemental active vitamin D metabolite/analogue usage and supplemental calcium dose <500mg/day by week 24 and changes in frequency of clinical symptoms of hypocalcaemia during weeks 16-24. The secondary endpoints were thought to be valid endpoints for proceeding to clinical trial.

Safety analysis focused on comparing the placebo group to those who had the drug and comparing adverse events, laboratory data, clinical episodes of hypocalcaemia and adverse events related to hypercalcaemia and hypercalciuria.

Changes in calcium, phosphate and CPP

There was a slight increase in serum calcium with PTH over the first 16 weeks but this settled down and did not go out of the normal range during the 24 weeks of the trial. Urine calcium dropped slightly with rhPTH(1-84) and then stabilised. The change in phosphate with the drug showed a significant decrease at the beginning of the trial that was maintained subsequently. The calcium-phosphate product did not change much for the placebo group at 24 weeks but there was a significant reduction in the CPP for patients treated with rhPTH(1-84).

RACE study design

RACE was the extension study that took the initial 24 weeks of data and examined that population over the next 6 years (Shoback 2018, Bilezikian 2019). The six years have just been completed. The subjects who were enrolled in the RACE study came from REPLACE and from the RELAY study. There were 49 subjects at the beginning of the RACE study and by the end of 6 years 34 subjects were still left in the study. During this time there was a stepwise increase in rhPTH(1-84) dosage from the starting dose of 25 or 50 microg to maintain target albumin-corrected serum calcium levels in the 8.0-9.0 mg/dL range.



rhPTH(1-84) therapy: approved by FDA and EMA (©Shutterstock)

In terms of the common treatment-emergent adverse events (TEAEs), what was seen in this extension study was similar to what was seen in the first six months. These were commonly symptoms related to hypocalcaemia or muscle spasms, paraesthesiae, sinusitis or headache.

Efficacy

The composite efficacy endpoint in RACE was >50% reduction in oral calcium (or <500 mg/day) plus >50% reduction in oral calcitriol (or <0.25 microg/day) plus albumin-corrected serum calcium maintained within normal limits. Reviewing the initial 12-month data, 76.1% achieved the composite endpoint; this percentage dropped a bit during the second and third year but then came back up to 70.0% at five years.

Conclusions

In the treatment of chronic HypoPT there are goals recommended by guidelines. The limitations of the current approach using calcium and active vitamin D are that if we give too much they can cause hypercalcaemia and if we back off too far, patients can get hypocalcaemia. Regardless of what we do with the serum calcium levels, obviously there is an effect on urine calcium. rhPTH(1-84) therapy is an adjunct that has been approved now by both the FDA and the EMA. Certainly it offers options for controlling hypercalcaemia and hypocalcaemia more effectively and it slightly reduces urine calcium.



Managing and optimising chronic HypoPT patients: Practical and clinical practice challenges

Professor Associate Professor Kalliopi Kotsa (Greece) and Bart L. Clarke (USA)

Workshop 5 discussed practical aspects and clinical practice challenges when managing patients with HypoPT. The first presenter was Associate Professor Kalliopi Kotsa (Thessaloniki, Greece). Not all patients with HypoPT are symptomatic but even those who do not have symptoms may have biochemical derangements.

The mainstay of treatment for acute HypoPT, post-surgical HypoPT and in chronic disease is calcium supplementation, usually calcium carbonate or citrate (Gafni 2019, Bilezikian 2016). Vitamin D is administered as calcitriol or alfacalcidol, and other measures include HCTZ which increases distal tubular calcium reabsorption. Phosphate binders and low-phosphate diets may be necessary if blood phosphate is high. Magnesium supplements may also be used.

Treatment goals are spelled out in management guidelines and are summarised below.

Ameliorate symptoms of hypoPT

- Maintain serum calcium within the low-normal range
- Maintain serum phosphorus within the high-normal range
- Avoid hypercalciuria
- Avoid elevated CPP

Fig 10. HypoPT patient treatment goals

(adapted from Shoback, 2008)

Any symptoms are to be improved. Biochemistry goals are to maintain serum calcium in the low-normal range, serum phosphate in the high-normal range, to avoid hypercalciuria and to avoid an elevated calcium-phosphate product. Blood and urine samples are used to monitor calcium, phosphate, magnesium, creatinine, 1,25 (OH)₂ vitamin D and urinary sodium. Renal ultrasonography at baseline will show whether the patient has nephrocalcinosis or nephrolithiasis.

Many patients on the standard care for HypoPT may be receiving either too much calcium and vitamin D or too little; in both situations the patient is at risk of complications. Brandi (2016) lists the criteria to identify those patients with chronic HypoPT who are not adequately controlled.

Case report

The patient was a 50-year-old woman operated on four years previously for a multinodular goitre. In 2016 she was taking large amounts of calcium carbonate, magnesium, alfacalcidol and L-thyroxine for HypoPT and hypothyroidism. Despite these treatments she was hospitalised a number of times with low calcium, high phosphate and very low PTH levels.

She was started on rhPTH(1-84). She improved to the point where biochemistry results were within the normal range and she had no need for either calcium supplementation or alfacalcidol. In addition, her mood improved hugely.

The second presenter was Professor Bart L. Clarke (USA). He commented that one caution with HypoPT treatment was that dose changes could not be made rapidly; at least 3-6 months of intensive effort on conventional therapy would be needed before consideration of change, and even then it was better to change one thing at a time. His patients generally felt about 80% better after starting PTH replacement therapy: the biochemistry improves but the quality of life improves a good deal.

The RELAY study

This study (Bilezikian 2017) tested lower doses of rhPTH(1-84), 25 and 50 microg doses, to see whether some patients could get by on these doses. The study duration was 8 weeks and the goal to maintain the same sort of triple end points that had been seen in the phase III clinical trial at a lower dose (Mannstadt 2013). Primary end points were not just a 50% dose reduction but they specified <500mg/day oral calcium dose, <0.25 microg/day of calcitriol and maintenance of albumin-corrected total serum calcium within the goal range. Secondary end points were the less specific 50% or more reduction in baseline oral calcium and baseline calcitriol with maintenance of the serum calcium.

Patients in both the dose groups achieved the primary end point, 21% of the 25 microg group and 26% of the 50 microg group (the difference between the two doses was not statistically significant). Some patients do take the 25 microg dose but they are uncommon.

rhPTH(1-84) has been available in the USA since 2015; the FDA gave approval based on the phase III trial results. We find that conventional therapy does not work well in some patients, and perhaps a third end up on Natpara mainly for clinical reasons but sometimes for biochemical reasons. Most of Professor Clarke's patients are generally taking 75 microg daily.

Patients' experience

Many patients adjust their doses on their own without necessarily telling their physicians. Patient associations provide support for patients who are poorly controlled, and a lot of information is available on the Internet beyond the medical setting. Some of this is not accurate or may not be the best information for that patient. As regards timing of the dose, those who take it in the morning sometimes feel that the dose has worn off by the following morning.

Doses of calcium

Physicians have to be very precise about what patients are actually taking, and the salt matters. Usually younger patients do well on carbonate and older patients tend to use citrate because absorption is better. In the USA HypoPT is largely a disease treated with calcium supplements whereas in Europe the tendency is to give larger doses of vitamin D and smaller doses of calcium supplements. The different approaches merit a research question.

Magnesium is sometimes an issue, as is potassium. These levels need to be monitored in addition to calcium levels.

Another aspect that adds complexity to management of HypoPT is co-morbidities such as viral gastroenteritis or upper respiratory tract infections. These can affect absorption of medications in the short term and therefore transient dose adjustments may be needed.



Monitoring HypoPT patients: Challenges in adhering to guidelines

Professor Neil Gittoes, UK and Dr Peter Kamenický, France

Workshop number 6 discussed monitoring patients with HypoPT, in particular the challenges in adhering to guidelines. The moderators were Dr Peter Kamenický and Professor Neil Gittoes.

Kamenický: how frequently should we assess calcium? Do we need to assess ionised calcium in symptomatic patients rather than just look at the albumin-adjusted calcium, and how frequently should we assess urinary calcium excretion?

Gittoes: we have spoken a lot about ionised calcium but practically it can be quite a difficult test to do in clinical practice.

Bollerslev: I think albumin-corrected calcium is a very robust measure that for daily clinic is good enough but there are situations where we do prefer to have ionised calcium. In my practice especially that is when patients are pregnant.

Kamenický: we have heard about the recommendations but a paper on real life monitoring of 120 patients with HypoPT was published by Mitchell in 2012. Patients in Boston, USA and Birmingham, UK were followed up for 7 years. Serum calcium was measured about 4 times a year, serum phosphate was measured approximately 3 times a year but only 44% of this cohort had at least one 24-hour urine calcium collection. It is a problem: patients do not like providing the 24-hour sample and perhaps doctors do not like asking for it.

Gittoes: you have inferred that although this is a highly specialised centre seeing these cases, still in terms of adherence to guidelines the results are not great.

Kamenický: some patients clearly are followed by GPs and a small fraction by nephrologists. The nephrologists would ask for 24-hour urine calcium samples much more frequently than endocrinologists.

Gittoes: I guess regionally, nationally and internationally we are trying to work in endocrine networks, with centralisation of services for patients with more difficult specialised conditions. We heard that about surgery but I think exactly the same management challenges face physicians as well.

Scans

Kamenický: another surprising aspect was that of the total cohort, 45% had at least one renal imaging but only 26% had a head CT scan. You could argue that maybe the majority of the cohort were post-surgical and maybe the brain calcifications are less frequent in this population, but still it is not a large proportion.

Bollerslev: if we diagnose a patient with idiopathic HypoPT we do a workup at baseline, which includes head CT.

Gittoes: I have concerns about screening tests when you do not really know how to interpret what you may see.

Sikjaer: there aren't many cases where there is a correlation between these calcifications and the symptoms that patients have.

Bilezikian: I don't think in a practice setting that head CT is all that valuable, in contrast to renal imaging. Every patient needs renal imaging even though there is no recommendation about which kind of imaging to use. Many of us would perform an ultrasound.

Kamenický: I try to do at least once a renal CT with injection of contrast because it really beautifully depicts the parenchyma of the kidney and is more informative than ultrasound. But this is more an opinion rather than relying on an evidence base.

Bone

Kamenický: The 2015 ESE guidelines (Bollerslev, 2015) advised against performing routine monitoring of bone mineral density (BMD) using DEXA scans. Yet the paper by Shoback (2016) showed that there are changes in the bone, in cortical thickening, an increase in trabecular volume and decreased bone remodelling that is probably due to PTH deficiency and maybe also to the effect of active vitamin D derivatives and their overtreatment.

Bilezikian: I disagree with that. My view is everybody who has HypoPT needs DEXA. Yes, bone density is typically above average but I have seen a lot of postmenopausal women whose bone density is not above average.

Gittoes: can I just pick up on the interesting point about postmenopausal women with

“When we discussed DEXA back in 2014 the data on fractures did not show an increase in fracture rate among patients with HypoPT . . . we need to look at this again, using more recent literature.”

HypoPT and low BMD. If rhPTH(1-84) is not available, how would you manage those patients?

Bilezikian: that is a very good question.

Sikjaer: if we do initiate rhPTH(1-84) we need to bear in mind that there is an anabolic effect in the spine, but in the forearm bone density keeps going down. For these cases this would be lifelong treatment and not just for 2 years, so it is something we need to think about.

Kamenický: (to Sikjaer) can you comment on two papers from your centre (Underbjerg 2014 and 2015) which looked at fracture risk in patients with both postsurgical and non-surgical HypoPT compared with controls. The total fracture risk was similar between patients and controls for both, but there was a decreased risk of wrist fracture in post-surgical patients and an increased risk of wrist fracture in non-surgical patients.

Sikjaer: we were surprised when we saw the results and we do not have a good explanation.



Importance of guidelines in patient management

Moderator: John Bilezikian (USA)

Faculty panel: Professor Jens Bollerslev (Norway), Professor Bart L. Clarke (USA), Professor Neil Gittoes (UK), Associate Professor Kalliopi Kotsa (Greece) and Dr Peter Kamenický (France)

The roundtable discussion on the importance of guidelines in patient management was chaired by Dr John Bilezikian, with faculty contributions from Professor Bollerslev, Professor Clarke, Associate Professor Kotsa, Professor Gittoes and Dr Kamenický.

Do we need guidelines?

Bollerslev: it is important we ask what literature evidence there is, review it critically and then take the evidence to the patients. We are giving guidance to our colleagues, and I definitely care whether the guidelines are followed. However, writing a guideline is a huge task: it took two years to do the last one and will take a year now to update it again.

Clarke: guidelines provide an opportunity to restate what the state of the field is, what the knowledge gaps are, and how best to spend our research dollars and efforts. Thinking specifically about HypoPT, before the first guidelines came out there was no clinical consensus.

Gittoes: another important point is that the purpose of guidelines is to improve patient care. Patients themselves benefit from access to guidelines that are simple and interpretable.

Kamenický: through guidelines experts talk to two different kinds of audience: they talk to each other and they also talk to the non-experts.

Bilezikian: I think there is great value in using guidelines to set a research programme as well as summarising what we know.

Time for guideline revision?

There are two sets of guidelines, which were very similar, published only a year apart but 5 years ago now. Do we need to consider a revision based on what has happened over the past 5 or 6 years?

Kamenický: I feel this is the right time. New data has been collected on PTH replacement therapy and on other aspects of the disease, such as bone health and the need for assessment of bone mineral density.

Gittoes: I think there is an opportunity for a refresh, although we still have not embedded what we think is important from the original. Let us do the basics well and let us not get distracted by writing something new.

Kotsa: for me the vague part of the previous guidelines was the quality of life. New guidelines will be necessary if we have new measurements of quality of life that can be widely used across most countries.

Clarke: by the time the literature review is done, the evidence has been accumulated and the document is written it will be five and a half years since publication of the previous guidelines. If you don't revise guidelines then you fall behind because the field has moved on.

Writing a new guideline

Bollerslev: there are different ways of doing this. You can have an international expert meeting and publish proceedings from that, which is a relatively fast process. Otherwise you can have task forces, write preliminary reports and convene an expert panel. The process that we have initiated is based on a critical update of the 2015 paper (Bollerslev 2015), so we are not starting all over again. By revising only the specific points needed, the timeframe for the new document is about a year.

The first thing you have to do is to define your research questions. We are going to look into risk of complications, for instance, and we are going to look into the evidence for new treatment algorithms, but we cannot just have an endless list of research questions. For each question we have to go into the literature and then update the guideline. Our first paper in 2015 was performed in collaboration with patient organisations and we also produced a patient leaflet and an emergency card that were translated into different languages.

Bilezikian: we have to get our information onto the Internet and it has to be the right information. It has to be translated into a document that patients can access.

Gittoes: we need a broader buy-in, that is where I think a lot of energy needs to be spent. Before getting into the detail about how we take it forward we really need to gather a group of stakeholders.

Bilezikian: there are many stakeholders and at least 20 important organisations internationally for accessing research. How far should we go in involving them up front?



Scientific literature (©Shutterstock)

Clarke: Trying to get everybody involved at the beginning with a lot of different agendas, such as government, industry and so on, complicates the process, and extends the time and budget needed. Whilst this approach may have greater credibility, it is quicker to do it through a scientific organisation or amalgamation of organisations to ensure the guidelines are not obsolete by the time they are finalised. It has to be a balance between time and effort. Maybe different approaches can be used at different times in the history of the disease or disorder. As HypoPT is a rare disease, in its infancy in some ways, maybe we are not yet at a level where we need buy-in from 20 different organisations before we start.

“We need to extrapolate through to the end product, which is benefiting patients”



Real-world data: How can we obtain new evidence to fill the knowledge gaps in hypoparathyroidism?

Professor Neil Gittoes (UK)

In the final keynote presentation Professor Neil Gittoes (UK) discussed how to obtain new evidence to fill the knowledge gaps in HypoPT using real-world data.

The main knowledge gaps in HypoPT are listed in figure 11 below. HypoPT is a rare disease so there are small numbers in many centres and the number of RCTs is small. We tend to rely on observational studies and case reports. We have spoken a lot about less than adequate, inadequate control. Conversely, we really don't know what optimal care is. We are grappling to work out what the long-term morbidities are in terms of renal, bone, quality of life. Can we improve management beyond activated vitamin D and calcium, and what is the place of PTH therapy.

Registries

What is meant by real-world data? The term refers to attempts to capture the practice that we deliver each day that then can be incorporated into a patient registry. So rather than an observational study at small scale, patient registries collect data that are uniform and that are specified prior to commencement of the registry. By collecting data in that way on that scale over a protracted period of time registries can shed light on the natural history of diseases, which is particularly helpful in rare diseases. That can inform views on efficacy and safety of treatments, and helps evaluate the impact of disease and treatments on quality of life measures. The impact of introducing a new treatment, its uptake, and how that can change outcomes for patients, can be judged. The impact of guidelines can be observed. Also, real-world data play a really important role in terms of governance and regulatory bodies, and evaluating the benefits and risks of new medicines.

However, registry data are uncontrolled and there may be confounders (Koltowska-Haggstrom 2017). The quality of data entry into a registry depends very much on resources, staff training and motivation; the data quality may not be as closely monitored as in RCTs. The bias can be high within registries because they provide naturalistic data. Any output from a registry has value but has to be treated with caution.

“I think PARADIGHM will provide excellent natural history data”

PARADIGHM

The PARADIGHM (physicians advancing disease knowledge in HypoPT) registry is a global prospective observational natural history disease and drug registry for patients with chronic HypoPT (Clarke 2018). It commenced in 2013, with a final report planned for 2035. It is really pleasing that we have this long-term tool that could shed significant light on the disease, looking for at least 10 years of follow-up experience in the majority of patients.

Objectives

The primary aims are to describe the long-term safety and efficacy profile of rhPTH(1-84) in patients with this disease. Pre-determined outcome measures include lab test results, renal function, soft tissue calcifications, fractures and cardiovascular events. The registry will not provide answers but it will fuel further discussions and probably fuel further hypothesis generation for us to study specific areas.

A secondary aim of PARADIGHM is to look at the natural history of the condition under conditions of routine clinical practice, again incorporating quality of life parameters.

Inclusion criteria for PARADIGHM eligibility are wide, incorporating adults and children with chronic HypoPT who are taking standard therapy and/or rhPTH (1-84). Routine medical care is captured by electronic case report forms, and quality of life measures using SF-36 in the adult population at baseline and continued through to help define the natural history. The study started in the summer of 2013, and baseline-recorded data are reported for 737 patients enrolled as of 30 June 2019.

Baseline demographics

At the data cutpoint, 134 patients were currently treated with rhPTH(1-84) and 603 had never been treated. Mean age was about 48 years, about 80% were female, about 84% were white and BMI was almost identical in patients aged over 18 years. There were perhaps fewer in the treated group where the primary cause of HypoPT is surgery.

Endocrinologists most commonly managed these patients. Thyroid hormone was the most frequently used concomitant medication in about 60% of both groups. The most commonly reported symptoms in the 6 months prior to study entry, such as fatigue, paraesthesiae, muscle twitching and cramping and headache, were more common in the currently treated group.

What about the impact on patients and therefore their utilisation of healthcare resources? Those who attended the ER more frequently in the 12 months prior to baseline were perhaps more likely to be on therapy. A similar picture pertained with regard to doctor's office visits within the 12 months prior to baseline. Perhaps targeting patients with greater need might give greater benefit.

What is optimal care?

- What is inadequate control?

What are the long-term consequences of hypoparathyroidism?

- Can we improve management beyond activated vitamin D and calcium:
 - Renal?
 - Bone?
 - Quality of Life?
 - Other?

Does replacement PTH therapy mitigate against morbidities in hypoparathyroidism?

Fig 11. Key knowledge gaps in HypoPT?

Summary

Deriving a secure evidence base in rare diseases is really difficult. As a consequence, registries are used extensively. They are appealing because of their scale and duration but we must be cautious as to how we use and interpret the data derived from registries. Specifically, I think PARADIGHM will provide us with some excellent natural history data and this is a key point. Registry data should be hypothesis-generating rather than trying to demonstrate causality. Of course, it will substantiate very long term safety monitoring of rhPTH(1-84).



Final panel discussion and Q&A

Moderator: Professor Jens Bollerslev (Norway)

Faculty panel: Professor Bart L. Clarke (USA) and Professor Neil Gittoes (UK)

The final round table gave faculty and the audience an opportunity to discuss all the material presented in session 3, on the management of HypoPT.

QoL and the PARADIGHM study

Audience: we have participated in the PARADIGHM study and recruited patients. We used the SF-36 (Short form health survey) and and now you have presented different tools that may be more appropriate for HypoPT. What are we to do about that?

Clarke: the SF-36 is what we had at the beginning six years ago but now we have three new ones with different levels of validation. I think this is something the PARADIGHM steering committee will have to address.

Bollerslev: what would it add to the registry if you put in a disease-specific questionnaire at a point when you have included all the patients?

Clarke: it would certainly give more precise information about the quality of life aspects that the SF-36 does not capture.

Bollerslev: what do we know about the patients who have not concluded the studies that have been presented in the past 24 hours?

Clarke: those data must be available and maybe the registry will address some of those questions but perhaps they will have to be looked at in a separate investigation.

Bollerslev: in open studies we are selecting increasingly those patients who feel the benefit of the treatment.

Clarke: there are also patients who have not been included in the clinical trials because their disease is not severe enough to need the treatment, or who do not meet the inclusion criteria or have exclusion criteria. There are still many questions about these patients.

Translating disease-specific questionnaires

Bollerslev: one advantage of the SF-36 is that it has already been translated into many languages and is accepted worldwide. The new disease-specific questionnaires will need to be translated into local languages.

Natural history

Bollerslev: do we need to know more about the natural history of the disease, as addressed in PARADIGHM?

Gittoes: I think we do need to know more. We do not have the evidence, certainly not at scale: the natural history that we are aware of is the experience that we pick up from seeing patients on an individual basis. It would be beneficial to capture the spectrum of expression of this disease.

Clarke: this will be hypothesis-generating. There will be observations coming out of this registry that we did not expect. It is hard for single-centre studies to address some of these aspects just because of the limitations of the rarity of the disease. The registry will shed a lot of light on these questions that will guide future research, so the agenda will keep changing because of the findings that are reported.

Gittoes: we have to be aware of limitations around registries and data capture and data quality. It is a really important point that registry data are really dependent on the individuals taking the time and energy to complete them accurately to generate meaningful data.

Audience: there is a clear need to collect evidence from more than one or two centres for the simple reason that HypoPT is a rare disease. These registries of long duration are essential to define the natural history. Secondly, improving the quality is an ongoing process. When working with data capture, validation and so on, the quality really improves when clinicians work together creatively, especially in rare diseases.

Beyond the registry, there are other tools to look at rare diseases and outcomes. In northern Europe the organisation of the healthcare system means that it is possible to find and track patients with a disease from birth to death, or at least long term for many years, and the richness of these databases is only now being investigated for rare diseases. There may well be more and more interest in this area of investigation. Lastly, the registry will give an opportunity to capture the practice in centres of excellence and to obtain additional information from there.

Gittoes: I think the primary driver for the registry is regulatory. Within the scientific steering committee there is significant scope for addressing questions that feed the natural history. In terms of the interaction with the sponsors we have great freedom in shaping and in interpreting and in presenting.

Future treatment of HypoPT

Bollerslev: the database runs to 2034. How will patients with HypoPT be treated at that time?



HypoPT: A brighter future? (©Shutterstock)

Clarke: because the data being captured are biochemistry, treatment doses and duration of treatment, I think at a very basic level they will give some insight as to whether too much calcium or too much vitamin D is not good for these patients. We will have a lot of information because we will have one third of patients treated with recombinant human PTH and two thirds not (on conventional treatment in relatively expert centres). We will be able to see what the outcomes are and maybe it will be very clear that substitution therapy with PTH works to spare patients complications, or maybe not, or maybe not all complications. You just have to wait a long time, for decades, for the accumulated data in order to say something strong.

Gittoes: over the timescale that we are discussing I would hope that interim analyses and parallel research studies will help to define a clearer core group of patients where it is unequivocal that PTH therapy is the way to go. The scale of that will depend on the clinical data and on access to the drug. As access to any drug becomes simpler then thresholds fall. I envisage that over the course of time we will have a clearer understanding of what suboptimal control is and how we can do something about it.

“.. the registry will give an opportunity to capture the practice in centres of excellence...”



Meeting summary perspectives

Professor John Bilezikian (USA)

In his closing remarks, co-Chair Professor Bilezikian thanked the audience and faculty for their contributions, before offering some summary perspectives from the meeting

Session 1. The biology of mineral homeostasis, imbalance and complications in hypoparathyroidism

- Treatment requires more than just normalisation of the serum calcium concentration.
- Complications in HypoPT are related, in part, to the duration and extent of biochemical disturbances.
- Patients with chronic HypoPT are at increased risk for renal co-morbidities.
- Elevated phosphate levels have their own adverse long-term effects.
- Pregnancies are high risk in these patients but some aspects of management are ameliorated.
- Indocyanine green (ICG) fluorescence angiography may be useful in predicting parathyroid function after thyroid surgery.
- A device that permits frequent calcium measurements at the bedside or at home would be welcome and is currently under investigation.
- Bone density and skeletal microstructure are abnormal but data are still sparse on fracture incidence.
- Brain dysfunction can be measured by new state-of-the-art dynamic testing.

Session 2. The inadequately controlled hypoparathyroidism patient

- In HypoPT, it is not always easy to define what is meant by good control.
- Biochemistry and perceived wellness are not necessarily concordant.
- Serious cardiac arrhythmias are possible in HypoPT, particularly in the setting of acute hypocalcemia.
- Several published studies using different instruments to measure quality of life concur that it is reduced in HypoPT.
- Studies are being conducted to assess capillary flow patterns and cognitive impairment.
- Replacement PTH therapy has shown beneficial results in terms of reducing needs for large amounts of calcium and active vitamin D.
- Avoidance of unnecessary neck surgery will help to reduce the incidence of post-surgical HypoPT.
- More data are needed on the natural history, including bone and kidney function.
- 24-hour urine collections are valuable but requested only infrequently.

Session 3. Management of hypoparathyroidism

- With advances in new knowledge, new guidelines are needed.
- The disease carries a significant burden.
- In the REPLACE study, more than half of patients on PTH therapy met the triple endpoint of reducing calcium and active vitamin D requirements by >50% while maintain the serum calcium concentration.
- In the extension study, efficacy was maintained.
- Albumin-corrected calcium is robust enough for use in most situations; the ionized calcium measurement is usually not necessary.
- Renal imaging should be performed in all patients but head CT is arguably less valuable.
- There are different views about the value of DXA testing in this disease.
- The ultimate aim of guidelines is to improve patient care.
- The PARADIGM registry should provide insights into the natural history of HypoPT and the efficacy of treatment.

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This independent summary report from the 3rd European symposium on Hypoparathyroidism, has been published by the European Society of Endocrinology, with the support of an educational grant from Takeda. All rights reserved © European Society of Endocrinology

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