

A FOCUS MEETING REPORT FROM:

1st Expert Workshop on Parathyroid Disorders

6-7 September 2018, Santpoort, The Netherlands

PARAT Steering Group:

Jens Bollerslev (Norway)

Claudio Marcocci (Italy)

Lars Rejnmark (Denmark)

Wim Van Hul (Belgium)

Camilla Schalin-Jäntti (Finland)

Andrea Giustina (Italy)

PARAT Expert Meeting Faculty:

Antonio Sitges-Serra (Spain)

Rajesh Thakker (UK)

Heide Siggelkow (Germany)

Hans Morreau (The Netherlands)

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Introduction

As Part of ESE's mission it is developing long-term educational programmes, projects and activities, defined around eight Focus Areas.

Within the Focus Area on Calcium and Bone, it is an exciting time to explore studies on the underlying pathogenic mechanisms of classical bone diseases, such as osteoporosis, as it increasingly becomes clear the role of bone tissue goes far beyond the obvious functions of the skeleton. Evidence is building to demonstrate that calcified tissue behaves as an endocrine organ, interacting with many other body systems, which makes its study of even greater relevance to many endocrinologists.

The publication of ESE's Clinical Practice Guideline on the Treatment of Chronic Hypoparathyroidism in Adults, which will be updated soon, has stimulated renewed interest levels in the scientific understanding of this specific area of endocrinology, and the new treatment options available. In recognition of this, our network of experts, key ESE stakeholders and existing committees have launched a new educational initiative entitled PARAT to develop ESE's focus around parathyroid disorders.



PARAT

PARAT is a programme of interlinked activities that will help define, explore and find solutions to unmet needs and challenges in the parathyroid disorders and calcium and bone areas. To achieve this we are using an activity framework made up of:

- Annual expert meetings
- Multi-media educational reports and communications
- Research activity and official publications

To deliver the objectives of the PARAT programme overall, we have appointed a dedicated Steering Group comprising:

- **Jens Bollerslev**, Steering Group Chair, Oslo University Hospital, Norway
- **Lars Rejnmark**, Aarhus University, Denmark (Clinical Lead, Focus Area on Calcium and Bone)
- **Wim van Hul**, University of Antwerp, Belgium (Basic Lead, Focus Area on Calcium and Bone)
- **Andrea Giustina**, San Raffaele Vita-Salute University, Milano, Italy, (ESE President-Elect)
- **Claudio Marcocci**, University of Pisa, Italy (ESE Clinical Committee)
- **Camilla Schalin-Jäntti**, University Hospital, Helsinki, Finland (ESE Education Committee Chair)

To kick off the PARAT activities, the Steering Group delivered the inaugural ESE Expert Workshop on Parathyroid Disorders just outside Amsterdam, on 6 September 2018. Together with renowned faculty, speakers and 20 invited expert participants from 15 countries, the group began identifying the most pressing challenges we face in parathyroid disorders.

This report synthesizes the workshop's research presentations and the valued opinions and insights from participants during the breakout sessions on Hypoparathyroidism, Primary Hyperparathyroidism and Parathyroid Carcinoma.

Welcome

On behalf of the European Society of Endocrinology and my fellow Steering Group colleagues, thank you for your interest in the inaugural ESE PARAT Expert Workshop, which set out to better understand such questions as:

- What are the main parathyroid disorder research issues?
- What are the most relevant priority parathyroid challenges we face?
- How can we begin to overcome such barriers to manage treatment more effectively?
- How can we deliver medical education to help satisfy such needs?

We are happy to report that in post workshop evaluation, 95% of our participants felt these aims would effectively enable experts and non-specialist endocrine communities to broaden their understanding of the topic. Whether an endocrinologist or endocrine surgeon, we look forward to your interest in our activities, helping improve the future care of patients.

I would like to thank my Steering Group colleagues, the faculty and speakers for developing our agenda, chairing, moderating, presenting in the sessions and for identifying expert participants to invite to the workshop. We look forward to inviting these colleagues to our 2nd expert workshop in the Summer 2019, along with further expert peers. We also thank ESE for helping us deliver the PARAT programme, and acknowledge and thank Shire for supporting it through a 2-year restricted grant.

Thank you for your continuing support of the PARAT programme.

Jens Bollerslev

Chair, ESE PARAT Educational Programme



PARAT Steering Group



JENS BOLLERSLEV
Norway



CLAUDIO MARCOCCI
Italy



LARS REJMARK
Denmark



WIM VAN HUL
Belgium



CAMILLA SCHALIN-JÄNTTI
Finland



ANDREA GIUSTINA
Italy

Workshop Faculty

Rajesh Thakker (UK), **Heide Siggelkow** (Germany), **Antonio Sitges-Serra** (Spain), **Hans Morreau** (The Netherlands).

Expert Participants

Natasha Appelman-Dijkstra (The Netherlands), **Karin Amrein** (Austria), **Zhanna Belaya** (Russia), **Marianne Catharina Astor** (Norway), **Filomena Cetani** (Italy), **Sabrina Corbetta** (Italy), **Richard Eastell** (UK), **Stefanie Hahner** (Germany), **Fadil Hannan** (UK), **Elif Hindie** (France), **Özer Makay** (Turkey), **Paul Newey** (UK), **Stefan Pilz** (Austria), **Lars Rolighed** (Denmark), **Federica Sapanaro** (Italy), **Tanja Sikjaer** (Denmark), **Kyriakos Vamvakidis** (Greece), **Peter Vestergaard** (Denmark), **Corinna Wicke** (Switzerland).



Become a PARAT stakeholder

Get involved at:
www.ese-hormones.org/parat

The PARAT programme is designed to adapt over time. By harnessing the valued perspectives of Steering Group members, workshop participants and other stakeholders, we will systematically build a programme that reflects contemporary parathyroid scientific research developments, and the day-to-day realities of practising clinicians. As we assimilate their knowledge, inputs and feedback from each completed activity, these will help us design and deliver new prospective elements, including:



Surveys, research audits and polls

To establish a base level of understanding from non-expert audiences, we are devising an initial online survey to send to ESE members and others. The member responses and stakeholder input will help us formulate parts of the 2019 Expert workshop agenda and other educational solutions in the future. Other continual feedback and research tools are deployed throughout the programme.



Calcium and Bone Digital Newsletter

Each Focus Area newsletter edition will feature insight and context from a different PARAT Guest Editor. Each edition will feature PARAT programme updates plus selected parathyroid disorder information from trusted resources to help increase understanding by non-expert endocrine communities globally.



ECE On Demand

Our online platform, hosting all permitted content from the European Congress of Endocrinology each year, offers users a deep archive of Calcium and Bone content including Hypoparathyroidism, Primary Hyperparathyroidism and Parathyroid Carcinoma. The PARAT programme will cross-reference with the most relevant ECE On Demand related abstracts, e-posters, webcasts and interviews.



Digital Updates

Various digital formats of workshops and future event summaries will be made available for expert and non-expert audiences via the website, social media and dedicated email campaigns.



2nd Expert Workshop on Parathyroid Disorders 27-28 June 2019 (TBC)

Following analysis of the 2018 workshop outcomes and survey supporting data, the Steering Group will shortly agree the agenda for the 2nd PARAT expert Workshop on Parathyroid Disorders 2019. The number of participants will expand to 50-60 persons, including all 2018 experts, plus 20-25 new invited participants based on their geographical location and career level. To be considered, please register here:

www.ese-hormones.org/PARAT.

Planned activity elements 2019.	
February:	PARAT Expert Workshop report distributed
	2nd Expert Workshop on Parathyroid Disorders announced
	Calcium and Bone Focused Digital Newsletter – Vol 1 2019
	Parathyroid Disorder ESE Members survey
May:	ECE 2019, Lyon; PARAT Update meeting – all welcome
June:	2nd Expert Workshop on Parathyroid Disorders. 27-28 June (TBC)
July:	ECE On Demand access to 2019 Parathyroid Disorders collection released
	PARAT review article publishes (Journal / Vol - TBC)
September:	PARAT Expert Workshop Digital report published
2020/21?	
Future PARAT programme activities will be announced in due course as funding levels are confirmed.	



Speaker: **Lars Rejnmark**,
Denmark.

CHALLENGES?

- **There is a need to achieve consensus on the definition of hypoparathyroidism (HypoPT) in order to assure appropriate treatment of patients**
- **We don't actually know the risk of HypoPT after neck surgery**
- **The impact of hypercalciuria is not well understood**
- **An intermittent high sodium intake may explain episodes of hypocalcemia**

Diagnosis and assessment of complications

Definition of HypoPT

Although experts and guidelines agree on the definition (HypoPT is a disease with low calcium levels due to inappropriately low or insufficient parathyroid hormone levels), this consensus does not hold true in the scientific literature, where many different definitions have been published.

A literature review¹ 8 years ago identified 10 different definitions of hypocalcemia in post-thyroidectomy patients. Depending on the definition used, the rate of hypocalcemia varied from 0–46% in the same cohort of patients. More recently, another literature review (unpublished) of review (unpublished) of papers published between 2010 and 2017 on the risk of permanent HypoPT following neck surgery was performed. The 89 papers identified used 20 different definitions of permanent HypoPT but none of these papers used the definition suggested by the different expert groups. The median prevalence was 2%, with a range from 0 to 20%.

In 2018 the American Thyroid Association published a statement² defining three different types of post-operative HypoPT.

- **Biochemical HypoPT:** low intact PTH levels below the lower limits of the reference range accompanied by hypocalcemia
- **Clinical HypoPT:** biochemical HypoPT plus symptoms and/or signs of hypocalcemia
- **Relative HypoPT, or parathyroid insufficiency:** clinical signs or symptoms of HypoPT that require medical treatment despite measured PTH values being within the normal range

Does it matter if patients have low PTH levels? Most of my patients with HypoPT have measurable levels of PTH, many within the lower limits of the normal range, but despite that they have severe hypocalcemia if they are not treated.

- It is the hypocalcemia result that matters rather than the measured PTH level

There is some uncertainty concerning the risk of HypoPT after neck surgery because it has been studied using so many different definitions that it is impossible to compare studies. Even worse, patients are not being correctly diagnosed. Many patients may be walking around with low calcium levels because the diagnosis of HypoPT is not being considered since their PTH levels are not below lower limit of normal (LLN).

Co-morbidities

In addition to hypocalcemia, HypoPT is associated with other biochemical abnormalities such as hyperphosphatemia and hypercalciuria, impaired quality of life, and an increased risk of a number of other co-morbidities such as renal impairment and renal stones, neuropsychiatric diseases and infections. Today's definition of hypercalciuria is calcium >7 mmol/24 h in females, >9 mmol/24 h in males, or calcium >0.1 mmol/kg body weight in both males and females. In the general population the prevalence of idiopathic hypercalciuria has been estimated to be 5–10%.^{3,4}

Most studies of renal calcium excretion in patients with HypoPT demonstrate an excretion of 7–8.8 mmol/24 h. Looking at the prevalence of renal excretion >7.5 mmol/24 h, the lowest figure published (Mitchell)⁵ was 26% but this is still 2 or 3 times higher than the general population. In Denmark we found the prevalence of hypercalciuria to be 56%.⁶

- Patients with HypoPT have a much higher prevalence of hypercalciuria than the general population

In the general population those with higher urinary calcium have an increased risk of renal stones.⁷ There seems to be a threshold: if urinary calcium is >0.11 mmol/kg/d then the risk of stones is significantly increased. How prevalent are renal stones in HypoPT? In studies using renal imaging, most report a prevalence in the range of 25–30%. Only a few studies have compared the risk of renal stones in HypoPT with the risk in the general population. We did that in our register-based study using ICD codes and found that the risk of renal stones is four-fold increased in such patients.⁸ These patients were hospitalised and symptomatic. In a recent study from Italy⁹ the odds ratio was 8.2 as assessed by ultrasound imaging, but most of these patients were asymptomatic.

How to treat hypercalciuria? We have thiazide diuretics, sodium restriction, PTH replacement therapy, changes in the dose of calcium and activated vitamin D. An experiment on the effects of oral sodium load for 10 days was published in 1982.¹⁰ It included 11 healthy subjects and 2 patients with HypoPT. After



being on a low-salt diet, they were all changed to a high-salt diet for 10 days. Urinary sodium and calcium increased significantly in response to the increase in dietary sodium in healthy subjects and HypoPT patients. Interestingly, in the normal subjects there was no change in the serum calcium levels but a slight increase in PTH levels in response to the increased salt load. In the patients with HypoPT there was a significant decrease in serum calcium levels.

- Patients with HypoPT sometimes have unexplained fluctuations in plasma calcium levels: could that in some instances be due to a very high intake of salt from snacks such as crisps?

How about PTH replacement therapy? None of the larger randomised controlled trials have shown any effect on 24-hour urinary calcium, no doubt due to the short plasma half-life of PTH after subcutaneous injection. It is unsatisfactory to give patients with HypoPT replacement PTH injections once a day: it should be given at least twice a day or preferably through a pump or maybe in the future we will be able to use long-acting PTH analogues. There are some initiatives ongoing developing such analogues. This might be the future but these molecules will probably be too costly for the majority of patients. Therefore we still have to address how to handle these problems in patients on conventional therapies with calcium and activated vitamin D.

Collection of 24-hour urine samples is troublesome to patients and to their healthcare providers. We have no good treatment for hypercalciuria and diagnosing hypercalciuria may cause anxiety to the patient. It is highly likely that hypercalciuria is associated with an increased risk of renal stones but most renal stones are asymptomatic and do not affect renal function. If you look more closely at the Danish study described earlier,⁸ the four-fold increased risk was based on 13 patients out of 688 during a median of 8 years of observation. If, following guidelines, the 688 patients had 24-hour urine collections made every second year for 8 years, a total of 2,752 urine collections would have been performed. We do not know whether this would have helped to prevent any of the 13 hospitalisations due to renal stones.

Biochemical control

A recently published paper on the importance of biochemical control for the risk of complications¹¹ was published recently. It was a case-control study aiming to assess indices of importance to risk of adverse outcomes in patients with HypoPT. The study included 431 HypoPT patients with a mean age of 41 years and a mean duration of disease of 13 years. The study showed that if ionised calcium levels are in the lowest tertile (<1.15 mmol/L) then there is a three-fold risk of cardiovascular disease. For high phosphate levels in the upper tertile there was an 8-fold increase in mortality and a 2-fold risk of infections. For calcium-phosphate product measurements in the highest tertile there was a 6-fold increase in mortality and a doubling in risk of renal disease. Maybe we need to treat our patients to keep the phosphate levels in the lower part of the reference range, though we do not know how to do that. For episodes of hypercalcemia there was a consistent association with all the assessed outcomes, and the same held for duration of disease. Although biochemical indices seem to be of importance to the risk of complications we are not sure how to address this.

"Does it matter if patients have low PTH levels?"

IN CONCLUSION:

- We need a consensus on diagnosis of HypoPT
- Most renal stones are asymptomatic
- It is questionable whether 24-hour urine collections are worth the effort
- We do not know whether improved biochemical control will lower the risk of co-morbidities



Speaker: **Heide Siggelkow**,
Germany.

CHALLENGES?

- Identify the best way to measure QoL and well-being quantitatively in HypoPT patients
- Evaluate influencing factors on well-being, like different forms and doses of vitamin D, calcium and magnesium
- Examine biochemical parameters influence well-being and QoL
- Correlate QoL with other complications of the disease
- Identify modalities to improve QoL in these patients

How well are our patients treated?

The patient journey

The typical patient journey in hypoparathyroidism (HypoPT) is not necessarily straightforward. As examples, after surgery the patient may experience anxiety, stress and pain due to symptomatic HypoPT. Additionally, the patient may go fruitlessly from one doctor to another until the diagnosis is made. Inadequate treatment once the diagnosis has been made may destabilise the doctor-patient relationship further. Patients may have problems with their medication due to side effects or they doubt the necessity for medication.

Some of the problems identified in primary care management include:

- Doctors may know little about the different forms of vitamin D
- They are not familiar with the goals of therapy as defined by the ESE guidelines
- They may not know about the side effects and complications of therapy
- Follow-up visits may not be frequent enough
- They do not measure the important biochemical parameters such as phosphate, magnesium and corrected calcium

There is no uniform approach across Europe for calcium prescription in HypoPT patients. Gastrointestinal symptoms are dependent on the amount of calcium that the patient takes, with diarrhoea in particular being more common when the patient has a calcium intake above 1 g/day.

The impact on patients' relationships and quality of life is extraordinary¹² The impact on their private lives is associated with a severe loss of personal self-confidence, as has been shown in questionnaires. Data also reveal a severe impact on work, with impairment and decreased concentration resulting in job loss and dependency on social security. In a Norwegian study, 40% of HypoPT patients received permanent or temporary social security benefits (SSB). This compares with 10% permanent SSB and 4% temporary SSB in the general population of Norway aged between 18 and 66 years.^{13,14}

One major problem is that we lack knowledge about the reason for the severe impact on quality of life and wellbeing in patients with HypoPT. The impairment may relate to the disease, its treatment, perception of the illness and the patient's general beliefs. We do not have data that compare the influence on wellbeing of different possible treatments.

Monitoring of biochemical parameters

One of the reasons for reduced wellbeing might be that patients are not well treated. We performed several studies to investigate the treatment situation in Germany one year after publication of the ESE guidelines. At the beginning of 2016 a one-page questionnaire about the management of HypoPT was sent to all German endocrinologists. Answers were received from 85 endocrine centres. The questionnaire included questions about their diagnostic workup and therapy, number of patients, and patients' laboratory values, treatment and follow-up. Calcium, phosphate and creatinine were measured regularly but calcium was not corrected for albumin in about 50%; PTH was measured in about 50%; and urinary calcium and magnesium in roughly 40%¹⁵. As regards the different forms of vitamin D, most patients were treated with calcitriol in combination with calcium but one third of the centres used alpha-calcidol and cholecalciferol. About 25% used magnesium therapy and 10% used thiazides.

A retrospective chart analysis of 711 patients from three centres was conducted, looking at medication, laboratory values and two clinical parameters, paraesthesiae and muscle cramps¹⁶ Parameters were analysed at first visit and during follow-up by an endocrinologist. The dose of calcium was mostly above 1,000 mg/day at first visit in these retrospective data but the dose decreased during care by the endocrinologist. There was no difference in the symptoms of paraesthesiae and cramps between males and females at first visit.

- The intensity of symptoms decreased visit by visit in both genders: treatment by an endocrinologist clearly does reduce symptoms
- Patients treated with calcium alone had the lowest serum calcium and the highest frequency of symptoms
- The lowest number of problems was seen in patients treated with alpha-calcidol and calcium
- Renal function improved from the first to the last visit
- No information was documented on other aspects of quality of life or work



Recommendations from the ESE guidelines¹⁷

- Aim at an adequate vitamin D status
- Provide information/education that enables patients to know about the possible symptoms of hypo- or hypercalcemia and complications of their disease
- Individualise treatment and measure the overall wellbeing and quality of life of the patient when implementing different therapeutic efforts

How should we do this? Reported symptoms that may affect the quality of life include physical symptoms (fatigue, muscle spasms, pain and paraesthesiae), cognitive symptoms (brain fog and inability to concentrate) and emotional difficulties (depression and anxiety).

Arlt¹³ used three different questionnaires to investigate complaints in 25 females with HypoPT. A global score of discomfort was increased significantly in patients compared to controls. Another paper¹⁸ reported that 65% of the respondents had peripheral cold sensations, 55% had pains in their joints, 55% had sensations of heaviness and weakness in the extremities, 45% had paraesthesiae, 40% had brittle nails and 35% had diarrhoea. Another study on epidemiology and health-related QoL in Norway¹⁴ used the SF-36 and the Hospital anxiety and depression scale (HADS). Compared to a normative population, patients scored significantly worse and, interestingly, the post-surgical patients scored worse than the non-surgical patients, especially on the physical health scales.

What about quality of life with PTH replacement therapy? Cusano¹⁹ found that after five years the SF-36 was better in a number of domains, both mental and physical. Another RCT looked at 62 patients with chronic HypoPT, who were randomised to six months of replacement therapy or placebo in addition to conventional therapy²⁰. The SF-36 questionnaire showed lower scores at baseline for the patients compared to a normative population; but they did not see a change after 6 months and the score did not correlate to BMI, age, duration of disease or aetiology of disease.

There are several possibilities to explain these results. Either the treatment does not influence QoL in these patients or there are effects on wellbeing but we are not able to measure them.

Differences in complications

Why do we see differences in complications between one study and another? In some studies patients are given higher doses of calcium; though most receive 1 g daily in the American study by Mitchell²¹ patients received 2 g daily. Similarly, different forms and doses of calcium and vitamin D are given from one country to another. In the Mitchell study the percentage of complications such as nephrocalcinosis and brain calcification is clearly higher than in European studies. By comparison, laboratory values are relatively similar. So the answer to the question may relate to differences in the study populations.

IN CONCLUSION:

- **The patient journey is not always straightforward**
- **Treatment by a specialist reduces symptoms and improves laboratory values**
- **Different study populations may explain the observed differences in long-term complications**
- **We need to identify modalities to improve QoL in these patients**

"Reported symptoms that may affect quality of life include physical symptoms: fatigue, muscle spasms, pain and paraesthesiae; cognitive symptoms: brain fog and inability to concentrate, and emotional difficulties: depression and anxiety."

Breakout discussion conclusions

BREAKOUT SESSION METHODOLOGY:

- All presentation sessions were followed by 75 minutes of breakout discussions. These were organized as 3 groups of 10 persons in each, led by a faculty moderator
- Each table discussion was recorded before the group's conclusions were aggregated together to reflect all participants views
- The concise summaries form an important part of future prioritisation of topics and activities for the remaining PARAT programme as a whole.

Definitions

Participants were struck by the many different definitions of permanent HypoPT. They agreed with the definition by ESE of low calcium levels with insufficient or inappropriately low levels of PTH. The ESE definition refers to 6 months but some delegates preferred a cut-off of 12 months to allow for recovery. Conversely, some patients actually develop HypoPT over time, when they get older, and do not have sufficient hormone production maybe years after surgery. An infection may trigger this, for example.

Post-surgical HypoPT

It is important to measure hypocalcemia in the diagnosis of post-surgical HypoPT.

- There is a great variety in treatment and follow-up during the immediate post-surgical period. We need data on prophylactic treatment at this stage. Age and renal function are relevant factors in recovery of bone quality
- When the post-surgical patient develops hypocalcemia it is also important to measure the magnesium and potassium because these can be treated
- How important is hyperphosphatemia? Further research is required to establish how important hyperphosphatemia and its management are since it is unfortunately less easy to treat than disturbances in magnesium and potassium

Parathyroid reserve

It would be good to find ways to define the parathyroid reserve. Perhaps a standard pre-operative measurement of calcium and PTH level might be considered in everyone undergoing extensive surgery who might have a risk of developing HypoPT afterwards.

Patient education

Some young patients have very variable dietary intakes, and this includes intake of salty snacks such as crisps

- Doctors need to tell patients that their diet is very important to keep their calcium levels stable, and that some of their calcium fluctuations can be due to changes in their diet

Further research suggestions

- We need more understanding about the cognitive impairment, and to find some explanation for the increased mortality observed in these patients. Ideally, patients would be asked briefly in clinic whether they have any issues with memory loss or sleep or feel depressed
- Can we prevent people becoming hypoparathyroid during surgery? Improving imaging or improving multidisciplinary care might help
- Participants would like better markers to measure the need for the skeleton to take up calcium more precisely
- A suggestion for next year's meeting is to have some paediatric colleagues because there are not any proper guidelines for how to handle children post-operatively

It might be useful to have discussions with paediatric endocrinologists to pool knowledge and discuss patient transition, as there is a period of time when patients are seeing both paediatric and adult endocrinologists.

Self-monitoring of calcium

The analogy has been sometimes drawn between type 1 diabetes and HypoPT. Is it possible to make a simpler, less expensive device to self-monitor calcium levels in very difficult cases? For doctors in the clinic it might also be helpful to have an immediate calcium level to advise patients so they can learn better when it is hypercalcemia, when it is hypocalcemia or if their symptoms are not related to calcium.

- Do we have any idea whether late complications are related to fluctuations in calcium? We know that the free or ionised calcium fluctuations in normal individuals are very low, that biological fluctuations are 1 or 2%. Calcium may be fluctuating more in our patients, and if that is related to late complications then its measurement might be of value. But that means that injection of PTH would also provoke fluctuations. If the hypothesis is correct, then it makes sense to have tighter regulation of the fluctuations in calcium
- It is also important to address these calcium fluctuations and their association with quality of life. For instance, you could look at the quality of life according to tertiles of average calcium levels

Pregnancy

Most of our patients with chronic HypoPT are post-operative. And those going through thyroid surgery are young fertile women who happen to become pregnant. How is this treated in pregnancy?

- We should try to gather some information on chronic HypoPT and also hyperparathyroidism in pregnancy and in the early puerperium



Speaker: **Rajesh Thakker**,
UK.

Parathyroid Carcinoma: A challenging diagnosis.

Parathyroid carcinoma (PC) is a rare disease: it accounts for less than 1% of patients with primary hyperparathyroidism (PHPT) in western countries though in Japan it is said to account for 5%. PC is usually a non-familial disorder, but may occur as a hereditary disorder as in the hyperparathyroidism-jaw tumour (HPT-JT) syndrome, which is due to mutations of the cell division cycle 73 (CDC73) gene, encoding parafibromin. It is typically diagnosed in the mid-40s, and patients present usually with complications of hypercalcaemia rather than tumour invasion or metastases.²²

Clinical features

The challenge is to distinguish PC from parathyroid atypical adenoma (PAA), but this is very difficult. There are no reliable clinical or biochemical features that are specific for PC. Prospective diagnosis of PC is important, as cure can only be achieved by complete resection of the tumours. Preoperative features suggestive of PC are a markedly elevated serum calcium with very high PTH 5-10 times the upper limit of normal (ULN). Patients may be relatively young, below 50, and because of the hypercalcaemia involvement of kidney or bone are seen in about 50% of patients. Unfortunately, these three factors are not really very helpful preoperatively in differentiating adenoma from carcinoma. A mass may be palpable in the neck, and rarely hoarseness presents because the recurrent laryngeal nerve is invaded.

Ultrasound scans may show heterogeneity, with calcification, infiltration and vascularity. A thick capsule should also raise suspicion. The sensitivity of these scans is about 80%, not really good enough for a firm diagnosis.²³

Pathological findings

En bloc resection of the primary lesion at the initial operation is the only curative treatment for this condition. If a simple parathyroidectomy is performed because the pre-operative diagnosis of PC has been missed, the local recurrence rates are significantly higher and survival much poorer. So this is dreadful news for the patient.

What may alert the surgeon to the possibility of a PC? A large tumour, usually >3cm; a PC may be firm, lobulated, grey and adherent to surrounding tissue. The tumour may have infiltrated the ipsilateral thyroid gland, strap muscles and other tissues; lymph node metastases are observed in 15-30% of cases.²⁴

The histopathology of PC is controversial.²⁵ Absolute criteria are invasion into adjacent soft tissue or vasculature, and documented regional or distant metastasis. Capsular invasion, fibrous bands and other features such as necrosis can be seen with large adenomas as well so the distinction is not clearcut. Up to 50% of patients present with metastases after an initial diagnosis of benign disease, implying that diagnosis is difficult.

The genetics of PC, including relevant testing

Germline mutations of *CDC73* are found in >75% of HPT-JT patients and also in 40% of patients with apparently sporadic PCs.²⁶ A patient with PC who has this mutation is at risk of the other tumours of the HPT-JT syndrome and the relatives are also at risk. So *CDC73* mutational analysis should be offered to all patients with sporadic PC and to their first-degree relatives as well, even if asymptomatic.²⁷

At least 20 genes are known to be involved in PC, and some of the genes involved could open up therapeutic pathways. The mutational signature of *APOBEC* is found in 30% of PC, and is associated with a high tumour burden and early onset of disease. These tumours with a high mutation burden may have an immunological reaction so you may be able to use immunological blockade to target those tumours. Other possible therapeutic options include epigenetic modulators, mTOR inhibitors and Wnt inhibitors.

What about the immunohistochemical markers?²⁸ There is loss or reduced nuclear expression of parafibromin in 70% of tumours. Reduced parafibromin expression correlates with an increased risk of recurrence and decreased survival rate. A lot of centres are exploring using combinations of different markers to improve diagnostic sensitivity and specificity. The other group of diagnostic biomarkers may well be microRNAs, which may prove a useful diagnostic adjunct.

The ratio of plasma PTH that is measured using third- and second-generation immunoassays is another intriguing marker.²⁹ PCs secrete a non-truncated amino-PTH which is recognised by third- but not second-generation immunoassays.

CHALLENGES?

- **Pre-operative diagnosis is difficult due to clinical features that mimic parathyroid adenoma**
- **Pathological diagnosis can be challenging as PC may resemble atypical parathyroid adenoma**
- **The diagnostic value of proposed biomarkers such as immunostaining is unclear**
- **There are limited treatment options for patients with inoperable disease or recurrence**

Treatment options and possibilities

Other than surgery, there are limited treatment options for those with inoperable disease or recurrence.

- Cinacalcet has been used for refractory hypercalcaemia in PC: it reduces PTH secretion by increasing the sensitivity of the calcium-sensing receptor. In one study this reduced the serum calcium from 15.0 to 11.2 mg/dl, and the patients with the highest baseline calcium levels had the greatest response. However, it may be associated with a number of adverse effects. The next generation is evocalcet, which has similar efficacy but perhaps fewer side effects³⁰
- Denosumab is a humanised monoclonal antibody which binds to RANKL and acts as a potent inhibitor of bone resorption. It is an option for patients with severe hypercalcaemia refractory to bisphosphonates and cinacalcet³¹
- PTH immunotherapy is another possibility. One group obtained symptomatic improvements and a lowering of serum calcium in a woman with metastatic PC after intradermal injection with synthetic human and bovine PTH fragments
- Adjuvant radiotherapy has also been used in some small series.³² The evidence suggests that postoperative radiotherapy may be beneficial in preventing PC recurrences. For example, 4 patients at the Mayo Clinic who received adjuvant radiotherapy because residual disease was suspected were alive, with no evidence of recurrence, at 60 months follow-up



"We have some medical therapies but we need some better ways to diagnose and treat the disease."

Future directions

We are not in a happy position, reports Professor Thakker. We cannot diagnose PC pre-operatively and we rely on surgeons to make the diagnosis. And when samples are sent to histology, we cannot sometimes categorically say whether the specimen is a parathyroid carcinoma. We have some medical therapies but we need some better ways to diagnose and treat the disease.

In summary, parathyroid carcinomas are a rare cause of PHPT and they mimic many of the clinical features of parathyroid adenoma. Surgery with en bloc resection of the primary lesion is the only curative treatment, and we need to get these patients to the surgeons with the correct diagnosis. Genetic testing for CDC73 mutations should be offered to all patients with PC as 40% of patients with sporadic PC will have this mutation.

IN CONCLUSION:

- **We need some better biomarkers to detect these tumours. Perhaps we should look at circulating tumour cells and circulating tumour DNA, multiple gene panels. No-one has done proteinomic or metabolomic studies in these patients**
- **We need to perform formal evaluation of parafibromin, Rb, CCND1 and galectin-3 to improve diagnosis and get a better idea about prognosis**
- **We need to perhaps validate the third:second generation PTH assay ratio, which seems quite promising**
- **As regards treatment, we need some well conducted clinical trials. Perhaps we should consider a trial of mTOR inhibitors, validation of PTH immunotherapy and other immune modulators. In addition, we could see whether temozolamide works. Plus we have access to epigenetic modulators; and 30% of parathyroid tumours have abnormalities of chromatin remodelling or epigenetics**
- **We need to work together to prioritise which of these we are going to test first**



Breakout discussion conclusions

Natural history

- We need to understand more about the pathogenesis and natural history of parathyroid carcinoma, including the triggers of PC, using cellular or animal models
- There is a CDC73 knockout mouse, which has abnormal parathyroids. In these mice the tumour has not metastasised, so this could be a useful model.

Registries and biobanks

- What is really needed for a registry is Europe-wide collaboration involving endocrine physicians and surgeons; part of setting up and using the registry would be to provide data and tumour material for mutational and histological analysis
- Many centres use the Eurocrine database, which was set up for rare endocrine tumours. This is now used by many clinicians for all thyroid and parathyroid cases
- A specialised registry, if possible allowing prospective follow-up of patients, was suggested

Diagnosis

- One problem is pathologists' lack of experience due to the small number of cases in some countries
- When difficult cases are encountered, consider consulting a reference / dedicated parathyroid pathologist to have a second look
- Exploration of the ratio between second and third generation PTH immunoassays is a field for further research
- Some thought that it would be advantageous to diagnose PC pre-operatively, though there was uncertainty about which test to use
- The other school of thought was that what we really need is peri-operatively to have an experienced parathyroid surgeon who can look at the features of the tumour and then carry out the appropriate surgery
- A pre-operative diagnosis will define where the patient is treated. Ideally the patient will be referred at that stage to a centralised and specialised centre

Ultrasound imaging

- It would be interesting to gather up PC images to look for signs suspicious of parathyroid cancer and to see how the disease evolves as shown on imaging

Centralisation

- We need skilled and experienced surgeons in the parathyroid field to deal with patients in whom there is a high level of suspicion of cancer
- Centralisation might be an advantage for the pre-operative diagnosis, for surgery, for pathology second opinions and for follow-up (perhaps within registries)
- There has been a big controversy finding numbers for certifying centres. Some people claim surgeons who can perform thyroid surgery automatically can perform parathyroid surgery, so this is where the discussion starts. In addition, the numbers always refer to benign disease rather than malignant disease. We have clear data to show that recurrence is much more common in non-specialised units
- Can we define which cases should be handled from the beginning in a centralised centre? Low-volume centres could miss patients with cancers. Some sort of expert opinion paper is very much needed

Making the diagnosis: pathologist, physician or surgeon?

- There seems to be a difference between the physicians' and surgeons' views of this condition. Physicians would prefer to diagnose PC reliably at an early stage, pre-operatively, but to surgeons this seems less of a priority. What you really need is an experienced surgeon to recognise the carcinoma at operation and then do the appropriate resection
- If a surgeon is trained in benign disease they may be able to spot malignant disease, but in a way it is too late if surgery has already begun; they should instead be aware of it pre-operatively
- What if the pathologist says to the surgeon that it is cancer once the tissue has been examined; will the surgeon go back? This sparked a lively debate. Some surgeons thought they were responsible for diagnosing the cancer, not the pathologist. Other participants thought that if a skilled pathologist says there is microscopic invasion of the adjacent tissue, you have to go back.



Speaker: **Jens Bollerslev**,
Norway.

CHALLENGES?

- Is trabecular bone preserved in PHPT?
- Trabecularisation of cortical bone in PHPT is potentially reversible
- For bone, it is safe to observe mild PHPT
- CV risk factors are reversible in PHPT
- Will disease-specific QoL questionnaires reveal the effect of PTH?

Bone metabolism and fractures, cardiovascular aspects, and quality of life

Trabecular bone

In PHPT, bone turnover is increased, with a reversible bone loss at the trabecular surface but a non-reversible loss at the cortical level. The remodelling space for the turnover of bone is increased; the resorptive phase is decreased; and also the depth of the resorption lacuna is decreased compared to normal individuals.^{33,34} Might this affect fracture risk?

Epidemiological and observational studies have demonstrated that fracture rate is increased in PHPT, and that significant bone loss, primarily at cortical sites, occurs with observation.

- Diagnosed osteoporosis with DEXA or the presence of low-energy fractures are regarded as indications for surgical treatment even in mild cases
- Surgery (or anti-resorptive medical treatment) will decrease bone turnover, filling the enlarged remodelling space and improve or normalise the observed increase in fracture rate

Based on histomorphometry, it seems that trabecular bone volume is maintained in PHPT but also that the trabecular space is enlarged due to a trabecularisation of the endocortical envelope, thereby thinning the cortical shell. Similarly, osteodensitometry data show the most significant decrease in bone mass in areas such as the forearm which are mainly cortical bone.

HRpQCT scanning has been used to compare the distal radius in patients with PHPT and controls.³⁵ In PHPT there is a separation of the trabeculae and a clear thinning of the cortical shell. And at follow-up, looking at both the radius and tibia, there is a clear negative correlation between PTH and both trabecular volume and trabecular thickness by BMD. The findings are similar for cortical bone volume. Similarly, a longitudinal study showed that most parameters improved in 29 patients with PHPT 24 months after parathyroidectomy, including cortical and trabecular BMD and cortical thickness.³⁶

- After surgery the bones actually increase their ability to absorb energy. In other words the trabecularisation of cortical bone, of the endocortical envelope, in PHPT is potentially reversible

Fracture risk in real life

A 2002 paper³⁷ looked at data from Danish registries and showed that bone fractures prior to surgery were increased in patients with PHPT and that the relative risk of fracture went down after surgery. The most recent study coming out of the same clinic in Aarhus looked at the prevalence of vertebral fractures in PHPT.³⁸ They identified about 800 patients with verified PHPT, of whom 588 had also an X-ray of the spine. These patients were followed for 10 years.

- About 22% of the total population of patients with PHPT had vertebral fractures

In the younger age groups of patients with PHPT (<50 years and 50-59 years), fractures were more prevalent in men than in women whereas in patients over the age of 60 years (and over 70 years) fractures were more common in women. The severity of the fractures was quite marked: 29% of patient had severe fractures whereas two thirds of the fractures were mild to moderate. When the patients with PHPT and fractures were compared to age-matched patients with osteoporosis, the patients with PHPT had a higher BMD compared to osteoporotic patients. So perhaps patients with PHPT might fracture at a higher bone mass level than patients with osteoporosis.

- Observational data and recent prospective randomised studies indicate that bone mass might become critically low with prolonged observation

Lundstam³⁹ described 5-year data in 191 patients who were randomised to either medical observation or surgery. About 120 patients completed the study. During observation there is no difference in the Z scores but with surgery you do have a significant increase in Z scores in the lumbar spine, to be expected since you are filling the remodelling space. In the hip, you similarly see an increase in the Z score with surgery but you also see a significant decrease in BMD: in the hip patients do continuously lose bone.

Charts of BMD in the lumbar spine, femoral neck, the proximal forearm, the distal forearm and total body at baseline and after 5 years of observation or after parathyroidectomy show a significant effect of surgery in all compartments except the proximal forearm. In the cortical bone in the proximal forearm there is no effect of treatment, raising the hypothesis that at the cortical bone level patients might not benefit from surgery in the 5-year perspective.



Altogether 5 new vertebral fractures developed in 5 patients, and they were all in the observation group. No patient in the surgical group developed a new fracture, and 5 patients did with observation. So, is it safe to observe patients with mild PHPT with respect to bone mass and potential fractures?

Cardiovascular risk

- Patients with PHPT do have insulin resistance and an increased cardiovascular risk
- They also have an increased BMI
- A positive effect of treatment has not yet been documented in patients with mild PHPT

Data from a Danish registry were used to investigate survival after surgery for PHPT. In Vestergard's first series³⁷ between 1979-1990 (mean age 60 years and 72% female, serum calcium 1.65 mM) the standardised mortality ratio (SMR) was 1.32. In a subsequent series from 1991-1997, with very similar ages and proportions of females but a slightly lower serum calcium, the SMR was not significantly increased.

- Is there is a threshold under which it is safe from the cardiovascular perspective to observe patients?
- As yet there are no significant findings from studies of biomarkers of insulin resistance and cardiovascular disease

Another study followed 958 elderly men for about 10 years.⁴⁰ There was a clear correlation between the hazard ratio for cardiovascular mortality and the PTH level. The conclusion was that elevated PTH accounted for about a fifth of the increased cardiovascular mortality although PTH over the whole spectrum gave no prognostic information even in the absence of PHPT.

The PTH level is directly correlated to the left ventricular mass index as determined by echocardiography. However, a meta-analysis of LVEF in PHPT⁴¹ before and after surgery did not demonstrate a significant treatment effect of parathyroidectomy on echocardiographic measures.

The third and fourth international workshops on hyperparathyroidism state that due to conflicting results cardiovascular disease is not considered to be an indication for parathyroidectomy in PHPT. Nonetheless, it would be interesting to investigate whether cardiovascular risk factors are reversible in PHPT and whether the culprit is PTH or calcium. Most probably it is both, but at different levels.

Quality of life

- Cognitive dysfunctions and impaired quality of life (QoL) have been found in patients even without specific symptoms but the effect of treatment has been ambiguous.
- Most experts do not recognise cognitive or psychiatric symptoms as an indication for parathyroidectomy⁴²

In chronic endocrine diseases, patients do have decreased QoL. Randomised studies have not shown clear effects on QoL whereas observational studies have shown an improvement after surgery. However, disease-specific questionnaires (PHPQoL) have recently been validated, and these may reveal a treatment effect of parathyroidectomy.

"There was a clear correlation between the hazard ratio for cardiovascular mortality and the PTH level."



SOME KEY QUESTIONS IN PHPT?

- How clinically relevant are the observed improvements in bone parameters after surgery?
- From the point of view of bone, is it safe to observe patients with mild PHPT?
- Are cardiovascular risk factors reversible, and is the culprit calcium or PTH?
- Does surgery for PHPT improve the QoL?



Speaker: **Claudio Marocci**, Italy.

CHALLENGES?

- How can the diagnosis of normocalcemic PHPT be secured?
- Risk factors for nephrolithiasis and the value of the “biochemical urinary stone risk profile”
- Why international guidelines are followed less than expected

Continuing diagnostic and management uncertainties

The clinical presentation of primary hyperparathyroidism (PHPT) has changed dramatically with increased accessibility to biochemical analyses. The diagnosis is today often made by chance in patients without specific symptoms, and silent nephrolithiasis may occur in up to 20% of cases.

Normocalcemic PHPT

Almost 20 years ago Rao postulated that in the process of developing PHPT the first abnormality would be an increase in PTH and the second phase would be an increase in serum calcium. So the only way to pick up the subclinical phase is to measure PTH in patients who have normal serum calcium.

Securing the diagnosis:⁴³

- PTH is consistently elevated
- Total albumin-corrected serum calcium is normal virtually all the time
- Most importantly, ionised serum calcium should be normal

At the time of evaluation before surgery, about 15% of patients with subsequently proven hyperparathyroidism have their total serum calcium within the normal range.

- Any cause of secondary elevation of PTH should be excluded before making the diagnosis of normocalcemic PHPT

To be excluded are: vitamin D insufficiency, renal insufficiency, gastrointestinal disorders that can cause malabsorption, drugs that interfere with calcium excretion (lithium and thiazide diuretics), hypercalciuria, and other known metabolic bone diseases. Low calcium intake can be responsible for an increase in PTH, and people with an increased BMI may have a higher PTH. But the most common factors are vitamin D and renal insufficiency. The cut off level of vitamin D that has been chosen to exclude secondary elevation of PTH is 30 ng/ml.

When faced with a patient who might have either normocalcemic PHPT or secondary hyperparathyroidism. We should make an effort when we are faced with such a patient to go back into the individual medical records to find measurements of serum calcium to assess whether there has been a change in calcium levels.

Is there a level of serum calcium at which you can say that an individual patient does not have classical PHPT? No, because we need to know the individual reference range if we are to answer this question.

Is there a role for imaging studies in refining the diagnosis? Studies seem to indicate that, among patients with normocalcemic PHPT, those with negative imaging do not develop significant changes in calcium or PTH on follow-up.

Risk factors for nephrolithiasis

Even though the profile of patients with PHPT has changed in the last 50 or 60 years so that we mostly see asymptomatic patients, a significant proportion are symptomatic for nephrolithiasis.⁴⁴ Silent kidney stones may be present in up to 35% of patients with asymptomatic disease. Hypercalciuria is an established risk factor for nephrolithiasis, and patients with PHPT and kidney stones have a higher urinary calcium excretion compared to those without kidney stones. However, some kidney stones in PHPT occur even in the absence of hypercalciuria so there may be other factors involved.

- The 2013 guidelines on asymptomatic PHPT⁴⁵ suggest performing an evaluation of the 24-hour urinary calcium (cutoff 400 mg/d) and increased stone risk by biochemical stone risk analysis in deciding which patients should be sent for surgery

A prospective study (unpublished data) performed between October 2016 and January 2017 included 176 patients with asymptomatic PHPT. In addition to the standard workup, 24-hour urine samples were collected for evaluation of several parameters. A computer program called Lithotest was also used, which can calculate the state of saturation for calcium oxalate and calcium hydrogen phosphate, the products which are usually present in stones in these patients. The aims of the study were to see whether hypercalciuria is associated with kidney stones in this population, whether 400 mg/d is the appropriate cut-off and whether the biochemical stone risk profile may give us something beyond urinary calcium.



Among the blood parameters, intact PTH and urinary calcium was higher in those with stones. None of the other parameters measured in the stone risk profile were different between the two groups.

Using the classical 400 mg/d only half of patients among those who have nephrolithiasis were positive and so the sensitivity is rather low although the specificity was acceptable. The positive predictive value (PPV) was only 32. Using the other cutoffs such as 4 mg/kg body weight or urinary calcium above 250 mg in females/300 mg in males, the sensitivity is improved but the specificity goes down and again the PPV is low. We are far from having an optimal measure.

Using multivariate logistic analyses for the parameters measured, the best association and best odds ratio would be obtained by combining calcium >4 mg/kg body weight and urinary magnesium <80 mg; the association of urinary calcium with calcium oxalate score gives a satisfactory increase in the odds ratio compared to the individual value.

In summary:

- The currently used cutoff value of 400 mg 24-hour urinary calcium in our guidelines has a rather low sensitivity and positive predictive value
- A positive stone risk profile has been found using Lithotest in patients who do not have increased urinary calcium according to the 400 mg cutoff
- The sensitivity can be increased using different cutoffs for 24 hour urinary calcium excretion but at the expense of specificity, and the PPV remains low
- The only way to increase the PPV in our series was to use 4mg/kg body weight as the cutoff value and to combine this definition of hypercalciuria with urinary magnesium below 80 mg or calcium oxalate product above 4 mg/kg

Following guidelines less than expected

Although all patients with symptomatic PHPT should go to surgery, this is not happening. For example, in a recent Californian series only half of those who were symptomatic underwent surgery.⁴⁶ About 42% of those with asymptomatic PHPT and who met at least one criterion, and interestingly about 20% of those who did not meet the criteria, went for surgery.

The Italian Society of Endocrinology recently designed and published a multicentre study⁴⁷ to identify patients newly diagnosed with PHPT and see how they were managed. In all 604 patients were identified and there are follow-up data for 345 patients at one year. Of the 158 symptomatic patients only 50% were submitted for surgery whereas the other half had not had surgery at the time of follow-up. Those who were submitted to surgery were younger, and had higher urinary calcium and PTH values. Among the 121 asymptomatic patients, again only about 50% of those who had at least one criterion for surgery were submitted for surgery. The total number who underwent parathyroidectomy was 152 out of 279 with a surgical indication.

We looked at the records of our patients and found that imaging studies were performed during the workup in 90% of patients independent of whether the patient was going to be selected for surgery. The presence of negative imaging studies was the major deterrent for surgery both in symptomatic and asymptomatic patients.

- Should guidelines for management of asymptomatic PHPT patients be revised?

"Using the other cutoffs such as 4 mg/kg body weight or urinary calcium above 250 mg in females/300 mg in males, the sensitivity is improved but the specificity goes down and again the PPV is low. We are far from having an optimal measure."

SOME KEY MESSAGES?

- **Normocalcemic PHPT is a diagnosis of exclusion**
- **Silent kidney stones are observed in a third of patients with asymptomatic disease**
- **The cut-off value of 400 mg urinary calcium per day used in current guidelines has low sensitivity and PPV**
- **Negative imaging studies are the major deterrent for surgery**

Breakout discussion conclusions

Diagnosis

- Is normocalcemic hyperparathyroidism a real disease or just a biochemical variant? More data are needed to refine this distinction
- Studies are needed on the natural history of the disease, following the patients over time to see whether they will eventually develop hypercalcemia
- Standardisation of PTH measurement seems to be an issue

We have to control our methods for measurement of ionised calcium and PTH. Each individual has set points for both calcium and PTH. An important point is to test the patient more than once before making the diagnosis

- ESE should inform colleagues and try to improve their education because so many doctors do not follow the guidelines. This is an important task for ESE

Measuring calcium

- Measuring ionised calcium is not that easy because factors such as sample pH and transport temperature can affect the results. "If you use that measure you should be really sure that your lab and system and methods of measuring work well"
- Ionised calcium should be measured using a point of care device, not in the hospital laboratory
- There was consensus that it is worth measuring ionised calcium in patients with normocalcemic hyperparathyroidism when possible

Individual set points

One way to investigate these is to go back into the medical records to look for previous calcium and PTH level measurements. Random variation between patients is wide but plots can be done with individual patients

- When the PTH is inappropriately elevated in relation to the serum calcium, this is an accepted criterion for the diagnosis of primary hyperparathyroidism

The individual set points may be related to the calcium sensing receptor but the data so far are underpowered

- Within the ESE we have probably got the numbers to build these data, which would be really useful.

Patient preferences

In patients, especially those with mild disease, it may be difficult for clinicians to persuade the patients to accept surgery. If the surgeon and the endocrinologist work together, that can be helpful because they can discuss different aspects with the patient.

- Patient preferences, and their reasons for choosing not to undergo surgery, should be investigated
- What is the appropriate follow-up for patients who refuse surgery?
- We should take patients' views into account in writing guidelines

Quality of life

- This should be an aim for future study in clinical trials

Guidelines

- Are the guidelines specific enough? This could be a subject for further debate
- Why are guidelines not followed?

Imaging

The main reason why patients were not referred for surgery was negative imaging, according to Professor Marcocci's presentation. It had much more relevance than the patient's symptoms. Such clinical practice is not in the guidelines so it is unclear how it has arisen.

Post-surgical supplementation

There is not a clear and consistent procedure and guidance for post-surgical calcium and vitamin D supplementation so everyone uses the approach of their individual centre.

- We might perhaps need some guidance from ESE on the recommended approach post-surgery

Should we be treating these patients with bisphosphonates after surgery or should we wait for a year and see what happens? Participants could not agree.



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Resources

ECE On Demand (2017 & 2018 content)

Search at www.eceondemand.org.

Search "Hypoparathyroidism" (62 content items)

Search "Parathyroid Carcinoma" (19 content items)

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Editorial team: Jens Bollerslev and PARAT Steering Group

Medical Writer: Dr Rachel Arthur

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On target

In post event evaluations, we asked our initial cohort of experts the question "How effective do you feel the planned 4-year PARAT programme of activities and methodology will be at improving parathyroid disorder treatment? To which 44.5% of participants thought it would be Effective and 52% said it would be Very Effective.

Their feedback, suggestions and the workshop conclusions are helping us to increase PARAT awareness across local endocrine communities.



Your view counts

PARAT's interactive programme is driven by the insight, experiences and priorities of its stakeholders.

To support the Steering Group, we urge you to do two things:

1. Complete the PARAT survey by 28 February 2019.
2. Share the survey link with your departmental, institutional or specialist networks, to gather as many views as possible.

Please complete the survey via any link sent to you from ESE or another Society no later than 28 February 2019, or via:

www.ese-hormones.org/parat



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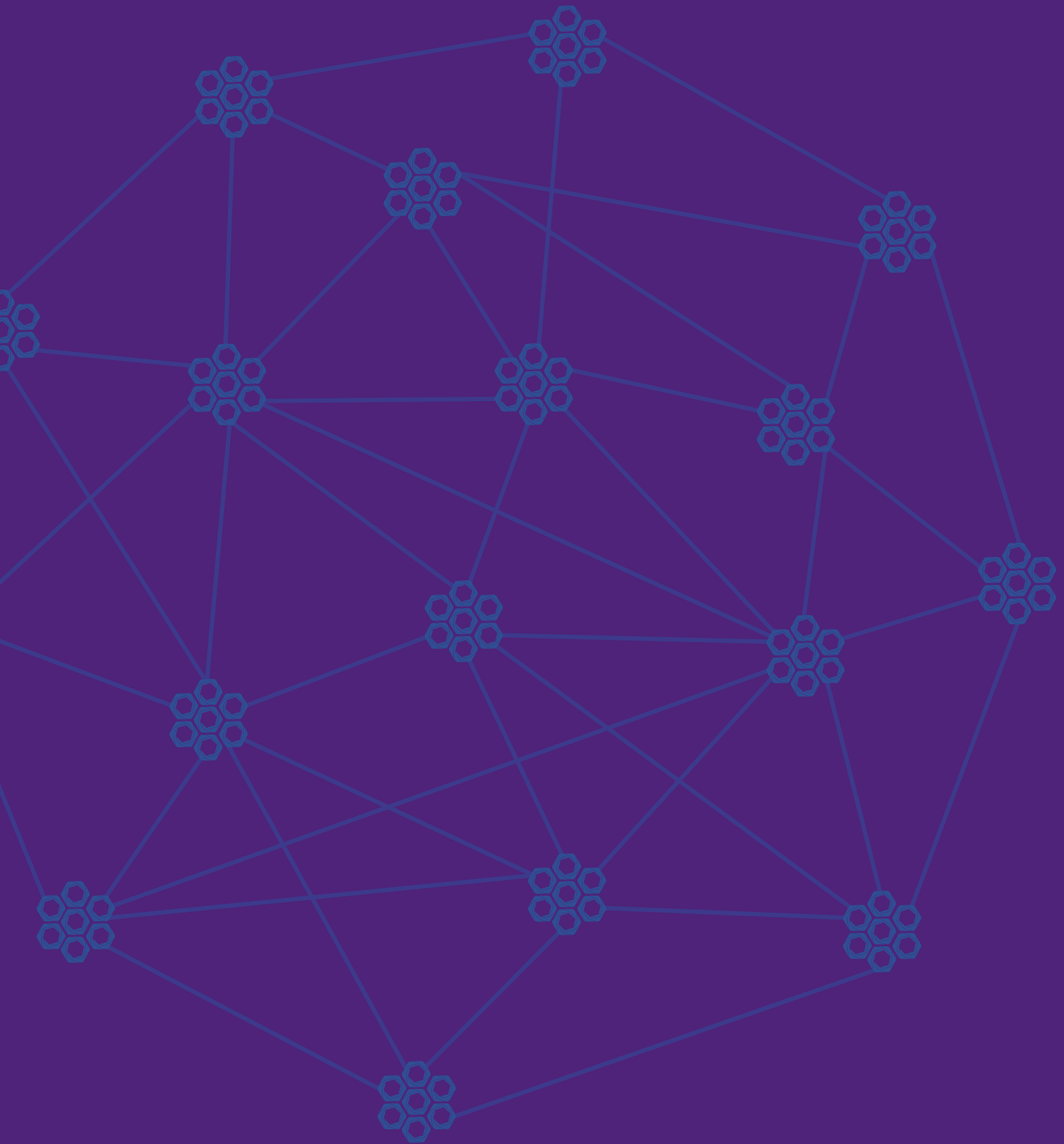
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