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Global Expert Summit on Hypoparathyroidism: Assessing and Managing a Complex Disease

20-21 November 2020
Online

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European Society of Endocrinology

The Co-chairs of the Global Expert Summit on Hypoparathyroidism (GESH 2020), are pleased to provide the international community with summary highlights of the event.

In an unprecedented year, our online event held over two half-days, 20-21 November, saw 200 international calcium and bone colleagues from 20 countries come together, to listen, watch and engage with the scientific programme and faculty.

This extended digital version and its condensed print edition, provide readers with a contemporary update on our discussions around hypoparathyroidism research, clinical management and future treatment needs..

The scientific planning committee thank the European Society of Endocrinology for independently publishing and distributing this report and also Takeda for their financial support of the online educational event and this summary.

Finally, we thank the invited faculty and attendees for their thought-provoking contributions.

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Insight

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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.

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Event Highlights

SESSION 1

Parathyroid hormone (PTH)

There are two main types of PTH receptor. The main PTH receptor, the PTHR-1, is expressed in bone, kidney and cartilage; it mediates calcium homeostasis and tissue development, coupling to multiple signalling pathways. The PTHR-2 receptor binds to a separate ligand, TIP39, and mediates neuroendocrine, pain and stress responses.

PTH (1-34) was mainly developed for the treatment of osteoporosis whereas PTH (1-84) is used as replacement therapy in patients with HypoPT. There is evidence for differential effects of these molecules in terms of intracellular signalling, on bone and on the vasculature.

The "classical" targets for PTH are bone and kidney. Whether PTH is a catabolic or anabolic agent depends on how it is exposed to the target organ. At the kidney PTH conserves filtered calcium and regulates phosphorus. PTH receptors are distributed widely in other tissues the body, including the cardiovascular system (CVS), the central nervous system, intestinal tract and the immune system. "Non-classical" effects of PTH may include those on blood pressure, endothelial function, cognition and neurological function.

The system of PTH, PTH receptors and receptorsome is complex. The potential involvement of the cardiovascular, metabolic and nervous systems deserve greater attention than they have received at this point.

SESSION 2

Complications and comorbidities

Renal failure is about three times higher in post-surgical HypoPT than in the general population. Patients with HypoPT cannot always be well controlled on standard therapy; hypercalciuria and nephrocalcinosis are common. Stone disease occurs in about 15% of patients. Distinct calcium sensing receptors exist in the kidney, and effects may be mediated by endothelin.

Chronic HypoPT is a two-hormone disorder affecting calcium homeostasis. Besides lacking PTH, patients are deficient in vitamin D activation.. Cardiovascular disease is increased in non-surgical HypoPT and is associated with disease duration in post-surgical HypoPT. Clinical studies suggest associations between HypoPT and increased pulse wave velocity (PMV), increased inflammatory myofibroblastic tumor (IMT), increased coronary artery calcium scores and arterial calcifications in the lower leg.

Glucose metabolism and diabetes are another area of importance in HypoPT. PTH replacement therapy may improve glucose metabolism and lead to a reduction in body weight through an increase in osteocalcin.

HypoPT is associated with depression and anxiety, and also with brain fog. These may be a result of capillary dysfunction in the brain, perhaps due to disturbed pericyte function.

Complications of HypoPT include changes in renal, vascular, glucose metabolism and psychiatric function, some of which may not be reversible with treatment

SESSION 3

The patient journey

Patients with HypoPT have reduced quality of life compared to healthy controls and reference populations. These effects seem to vary by age and gender: biochemical parameters, aetiology of disease. Treatment may be influential.

The data on mortality are sparse and the results are not consistent. Cardiovascular autonomic neuropathy is increased, and might be a new parameter to investigate. Patients may have increased risk for vertebral fractures, even if they have high BMD. The risk of infection, and developing frequent infections, may be increased; the most common infections are UTIs. Changes in monocytes, lymphocytes and NK cells have been demonstrated.

In patients with Covid 19, hypocalcaemia is a strikingly frequent finding, which can be predictive of the severity of the disease.

Low levels of vitamin D have been correlated with higher risk of Covid 19 and disease severity. Patients should be evaluated for vertebral fractures, which can be correlated to the clinical outcome

Nephrocalcinosis and soft tissue calcifications may occur in HypoPT. A nutritional history should be taken. Phosphate additives in food, used to prolong shelf life, may be 100% absorbed.

Diabetes and HypoPT may co-exist. With rhPTH (1-84) better glucose control may be obtained.

Pregnancy duration is slightly shorter in women with HypoPT and preeclampsia is more common but the overall risk of adverse pregnancy outcomes is low.

SESSION 4

Evolving goals and guidelines

Conventional therapy focuses on calcium and active vitamin D but it is often difficult to obtain adequate control of serum calcium. Studies with rhPTH (1-84) have established its efficacy in restoring mineral metabolism, in improving skeletal and renal indices, and in improving quality of life.

Is it time to create a global guideline for the management of HypoPT? Much new information has been gathered but this does not necessarily translate into changes in management. Information on costs is needed also.

Potential issues that need more thorough investigation when patients are first seen include glucose tolerance, infectious disease risk and dietary history. Patients should be helped to improve their self-management skills. A major agenda item relates to understanding where recombinant human PTH fits into the treatment paradigm. This is also relevant to other PTHs on the horizon.

PTH receptors: Where are they and what do they do?

Speaker: Prof. (Assoc) Thomas Gardella *(USA)*

PTH receptors are integral membrane proteins that bind an extracellular peptide ligand to activate signalling responses in target cells, changing the properties of those cells. In humans there are two types of PTH receptors. The main PTH receptor that mediates the classical actions is the PTH receptor type 1 (PTHR-1). It binds PTH as well as PTH-related protein (PTHrP) and it mediates the endocrine control of calcium homeostasis via PTH and the paracrine control of tissue development via PTHrP. This receptor is expressed in bone, kidney, cartilage and other tissues. The second PTHR-2 receptor binds a separate ligand, TIP39, and it mediates neuroendocrine, pain and stress responses and the development potentially of other tissues such as the testes.

The PTHR-1 is a class B G-protein coupled receptor (GPCR) is related to the receptors of calcitonin, glucagon, GLP-1 and several other peptide hormones. The C-terminal 15-34 portion of the ligand interacts with the extracellular domain of the receptor and the N-terminal 1-14 section of the ligand interacts with its transmembrane region.

The PTH receptor couples to multiple signalling pathways (Bastepe 2017). The main pathway that mediates most of the biological responses to PTH involves the alpha s subunit of the G-protein which activates adenylate cyclase leading to increased formation of cAMP, activation of protein kinase A and downstream effects in target cells. For example, in bone cells it downregulates the expression of sclerostin.

In the kidney, PTH receptor signalling modulates the expression of genes involved in the synthesis and metabolism of 1,25 dihydroxyvitamin D. In the proximal tubule of the kidney, it downregulates the expression of sodium-dependent phosphate transporters 2a and 2c, leading to excretion of phosphate into the urine. In addition, PTH receptor signalling modulates calcium channels leading to reabsorption of calcium from the filtrate.

These actions are mediated for the most part by PTH ligands whereas a response to PTH occurs during development, particularly in the growth plates.

Given this complex biology, it is not surprising that a number of mutations have been identified in the PTH-1 receptor and also in the ligands that cause disease although these are all rare.

Evidence for a new pathway that mediates actions of the PTH receptor in bone cells has recently been identified to involve the salt-inducible kinase (SIK) proteins, and by this pathway PTH receptor signalling leads to activation of protein kinase A (Wein 2018). Transcriptional modulators are translocated into the nucleus, where they bind to their respective promoters: Receptor activator of nuclear factor κ B (RANK) ligand leads to bone resorption whereas the host promoter leads to an increase in bone formation.

The role of this pathway is illustrated dramatically in mice that have SIK2 and SIK3 knocked out specifically in osteoblasts and osteocytes (Nishimori 2019). These cells show a large increase in total bone in the trabecular region. These effects can mostly be explained by an increase in bone mineralisation.

PTHR-1 is expressed in renal proximal tubule cells. Receptor can be detected at the basolateral or blood side of the epithelial tubule cells and at the luminal side (Amizuka 1997). PTH actions on these receptors leads to the downregulation of the transporters. These cells could potentially respond to PTH ligand that has been filtered into the urine. The PTH receptor can also be detected in the vessels of the kidney, and evidence for a physiological function of these receptors in the renal vasculature is shown in studies performed on perfused isolated rat kidneys (Eschinger 2002).

PTH receptor signalling also leads to hypotensive effects systemically. This has been seen in experiments in mice that expressed either the wild type PTH receptor or a phosphorylation deficient receptor, a mutant, that leads to enhanced cyclic AMP response in this receptor. Mice that expressed that mutant receptor, compared to wild type mice, show an exaggerated hypotensive response. There is also evidence that PTH receptor signalling can cause hypertensive effects. This comes from epidemiological data where patients with hyperparathyroidism have been observed to have hypertension.

PTH receptor as well as PTHrP ligand have been detected in brain (Weir 1990). However, the role the PTH receptor might have in the brain is still unknown.

There is also evidence that cells in the immune system express PTH receptors. This comes from work where the PTH receptor specifically was knocked out in T cells in mice. Thus, there is evidence of cross-talk between cells of the immune system and cells of bone via PTH 1 receptor signalling.

The PTH2 receptor mediates neuroendocrine actions via the ligand TIP39. The receptor is 51% identical to the PTH1 receptor at the protein level, and is expressed in brain, the vasculature, pancreas, testis and kidneys. The functional TIP39 ligand is expressed in the brain, particularly the hypothalamic region. The functional role of the PTH2 receptor has been addressed using mice with knocked out receptor. The phenotype is a gender-specific effect so that males are sterile due to a defect in spermatogenesis and the females have an impaired lactation response.

Key Learning Points:

- **The PTH1 receptor is a class B G-protein coupled receptor expressed in bone, kidney and other tissues**
- **Mutations cause diseases of bone and calcium metabolism**
- **SIK is a recently regognized downstream mediator**
- **PTH2 and TIP39 have no known neuroendocrine or development functions**

Differential effects: PTH and analogues at receptors?

Speaker: Prof. Erik Fink Eriksen *(Norway)*

PTH (1-34) was mainly developed for the treatment of osteoporosis. The rapid, 3-hour peak of pharmacokinetics was associated with maximal anabolic action. PTH (1-84) has a much longer half-life result in protracted action, mainly in the kidneys. Both analogues can safely be used for osteoporosis (Bilezikian 2018).

There are several types of PTH receptors. The two main subtypes are the PTH1 receptor which predominates in the classical target tissues, bone and kidney. They have a preferential sensitivity to N-terminal fragments. The PTH2 receptors predominate in the CNS, thyroid, G-I tract, pancreas, vasculature and testis. PTHrP does not activate the PTH2 receptor. The PTH2 receptor is activated by a specific peptide called the tuberoinfundibular peptide, TIP39. TIP39-expressing neurones match PTH2 receptor distribution in the brain in neuroendocrine centres. The periventricular, paraventricular and arcuate nuclei contain the highest density of PTH2 receptor positive networks.

The PTH2 receptor modulates the stress response, corticosteroid release, anxiety state of animals, the fear response and stress-induced analgesia (Dobolyi 2012). It also is associated with release of arginine vasopressin and growth hormone, thermoregulation, nociceptive information processing and prolactin release during lactation. It is associated with inhibition of chondrocyte proliferation and differentiation. The C-terminal domains of the receptor seem to be responsible for antioxidant effects of PTHrP in osteoblasts, and TIP39 has been shown to promote wound healing. The PTH2 receptor is also expressed in human leukocytes.

The vast majority of studies have addressed the effects of the N-terminal fragment but there are possible effects of the C-terminal fragment. Animal data suggest that a specific C-terminal receptor exists (Murray 2005), but such intriguing studies have yet to be translated into definitive concepts of actions of the C-terminal portion of PTH. Some ideas about the actions of the C-terminal of PTH, and these are reviewed by Murray (2005). The parathyroid gland in normal circumstances releases intact PTH (1-84). The release is modulated by ionised calcium binding to the calcium receptor on the parathyroid cells. There is a release of C-terminal fragments, which on a molar basis outweigh the intact hormone secretion by a factor of 5. And this secretion is stimulated by ionised calcium, contrary to the inhibition seen with intact PTH. These fragments are filtered through the kidney but they may also act on C-terminal PTH receptors in bone. The intact PTH is metabolised in the liver, and only C-terminal fragments are released. These may also act on C-terminal PTH receptors in the bone. By binding to C-terminal PTH receptors, these peptides may inhibit calcium release from bone, counteracting the active calcium release from bone by the PTH1 receptor.

Turning to bone and calcium from human studies (Piemonte 2009), after a single injection of PTH (1-34) versus PTH (1-84) there is a trend to an earlier increase of serum calcium with PTH (1-84) compared to PTH (1-34). In terms of stimulation of 1,25 hydroxylation of vitamin D there is not much difference between the two peptides; however, PTH (1-34) leads to a reduction in urinary calcium whereas it remains unchanged after stimulation with a single injection of PTH (1-84).

A study by Rejnmark and colleagues (Bislev 2014) looked at changes in calcium homeostasis in HypoPT patients transitioning between PTH (1-34) and PTH (1-84). When patients went from conventional therapy to PTH (1-84), the alpha calcidiol dose was reduced by 88% and calcium intake levels by 78%.

When patients had to be switched back for a while from PTH (1-84) to (1-34), there was a drop in serum calcium. There was a need for increased calcium supplementation by >300mg on average, and for an increased active vitamin D dose. However, the two doses were not equimolar. This is a problem in many studies.

PTH is also vasoactive and a study on bone resistance arteries (Benson 2016) showed that PTH (1-34) had a smaller effect on maximal dilation of these vessels, far less than what was seen with PTH (1-84) and PTHrP.

A recent study from Amsterdam and Denmark (Hansen 2013) used high-resolution quantitative computed tomography (hrQCT) to look at bone changes and bone turnover markers after giving either PTH (1-34) or PTH (1-84). There was not much difference in terms of increase in BMD in the lumbar spine. At the total hip PTH (1-84) gave less of an increase. At the distal forearm, which is mainly cortical bone, the two peptides had about the same effect.

When it comes to hrQCT data looking at cortical thickness and porosity, there is a huge difference both in the radius and tibia. There is an increase in cortical thickness with PTH (1-34) while there is either no change or in the tibia an actual decrease with PTH (1-84).

Key Learning Points:

- **There are differential effects of PTH (1-34) and PTH (1-84)**
- **There may be a relationship between the PTH2 receptor and CNS symptoms**

The complexity of parathyroid hormone: Classical targets

Speaker: Prof. John Bilezikian *(USA)*

There have been some recent new concepts on how PTH could be an anabolic agent for bone, and three of these have been reviewed (Dempster 2020). The first is the accrual of bone on surfaces that have already been remodelled, remodelling-based bone formation (RBF). Another kind occurs when PTH directly stimulates lining cells on quiescent surfaces, modelling-based bone formation (MBF). The third mechanism (oMBF) relates to an overflow of bone formation based on the initial bone remodelling unit.

Dempster (2017) performed a study looking at individuals who were going to undergo hip replacement for osteoarthritis. They were given teriparatide 20 mcg daily for 6 weeks or so prior to surgery, and then they were given tetracycline labelling after they began the teriparatide so that at the time of surgery a sample of the femoral neck could be obtained for analysis. The study found that the predominant early anabolic effects of teriparatide are due to bone formation on pre-existing remodelling units at the cancellous and endocortical surfaces.

With regard to PTH in the osteoblast, we know that it reduces osteoblast apoptosis and it increases the signalling pathway that is classically associated with bone formation, namely wingless-related integration sites (Wnt). PTH also has very important effects on the osteocyte, and the thought is that PTH is an antisclerostin agent. Again by that mechanism it can lead to stimulation of the Wnt signalling pathway.

If this were a pure anabolic agent what we would see would be bone formation exclusively being stimulated, and that is not the case either with teriparatide or with any other anabolic agent that we have. A review article by Wein and Kronenberg (2018) discussed the factors that converge and are complementary to the actions of PTH as an anabolic agent.

There is more to PTH's anabolic actions when it comes to stem cells, bone marrow stromal cells and the mobility of osteoblast precursor cells. In work done by Fan (2017), PTH was administered and the fat cell content of marrow was examined. PTH shifted the lineage pathway from the adipocyte to the osteoblast. PTH also has important actions in recruiting precursors of osteoblasts in the circulation (Rubin 2011).

The actions of teriparatide are limited in reality. First stimulation of bone formation but then eventually bone resorption is evident (Tabacco 2019). That increase in bone resorption probably limits the anabolic potential of PTH. Over time bone resorption exceeds bone formation and under the influence of PTH catabolic actions are observed. Under certain conditions PTH will serve as a catabolic agent through RANK ligand, stimulating bone resorption.

In the kidney the physiological action of PTH is to conserve filtered calcium. In the cortical thick ascending loop of Henle it uses a co-transporter to reabsorb calcium and in the distal convoluted tubules it helps to regulate renal handling of calcium.

The first step in the activation of vitamin D, namely the hydroxylation of vitamin D at the liver, does not have many control mechanisms but during the second step a number of factors such as PTH help to facilitate the action of the 1 alpha hydroxylase as well as a reduction in the serum phosphorus. Other regulators will lead to a reduction in the conversion of 25 hydroxy vitamin D to 1,25 dihydroxy vitamin D, including calcium itself, the end product 1,25 dihydroxy vitamin D and FGF-23. A very interesting complex interplay at this particular biochemical step will either lead to a facilitation or restriction of active vitamin D formation.

Another important issue relates to how phosphate is regulated (Berndt 2008). Regulators include phosphate itself, PTH, vitamin D and FGF-23. And the regulation of phosphate is certainly a feature of the renal actions of PTH using the sodium-phosphate co-transporter. In HypoPT, because there is not enough PTH, phosphate is not effectively cleared in the kidney, and that explains why the serum phosphate level rises.

As regards vitamin D regulation of phosphate, the actions of 1,25 dihydroxy vitamin D are thought to increase NPT2b transporter expression leading to increased phosphate absorption in the G-I tract. At the kidney 1,25 dihydroxy vitamin D is thought to increase expression of this transporter leading to reabsorption of phosphate and in bone 1,25 dihydroxy vitamin D will stimulate bone resorption over bone formation in the setting when phosphorus is low.

Another player to consider is FGF-23 (Jueppner 2011). FGF-23 is a product of both the osteoblasts and osteocytes. It increases renal phosphate excretion and reduces the expression of renal 1 alpha hydroxylase. FGF-23, PTH and 1,25 dihydroxy vitamin D all work in a very complex way to regulate each other.

Key Learning Points:

- **In bone PTH regulates bone modelling and remodelling**
- **PTH can be either anabolic, catabolic or both simultaneously**
- **In the kidney PTH regulates calcium and phosphate**

The Complexity of parathyroid hormone: Non-classical targets

Speaker: Prof. Maria Luisa Brandi *(Italy)*

PTH and its receptors form a pleiomorphic system. PTH 1 mediates several actions through second messengers. The PTH 2 receptor mediates the action of TIP39 and is activated by PTH in humans. And finally the PTH type 3 receptor is absent in mammals but is present in zebrafish (Ehrenmann 2019).

The PTH1R and PTH2R receptors are widely distributed in the body (Tian 1993). They are present in many different systems such as the secretory and excretory glands, the nervous system, skeletal muscle, intestinal tract, reproductive system and also the immune system so PTH can have an impact on all these organs.

When PTH receptor type 1 is activated by peptide, a number of different second messengers and a number of different proteins can be activated or inactivated through the formation of cell-specific receptorsome complexes with cytosolic constituents. These could be the basis of the differential actions of PTH in different tissues.

As regards the cardiovascular system, it has been demonstrated that PTH has a number of actions. They include effects on cardiomyocytes, effects on the RAAS, actions directly on the blood vessels and actions also on glucose and fat metabolism. Primary hyperparathyroidism creates various disturbances, not only the increase of PTH but also the increase of calcium. And calcium per se has an impact on cardiovascular function. So there are various effects that the hormone has, like increasing blood pressure, creating problems in terms of glucose metabolism, increasing chronotrophy and hypertrophy of the cardiac myocytes, and on the other side calcium has effects on endothelial function and on aldosterone. The interaction between calcium and PTH influences cardiac function and also cardiac trophism.

Sometimes the cardiovascular system is the first manifestation of primary hyperparathyroidism. In unexplained LV hypertrophy, calcium and PTH should be measured.

In HypoPT the majority of effects to be seen at the cardiac level result from the hypocalcaemia. That is QT prolongation, alterations that predispose to arrhythmias, cardiovascular autonomic neuropathy, dilated cardiomyopathy, lowered cardiac contractility, an increase in glucagon secretion and also cardiovascular calcification. And PTH-dependent cardiac effects may lead to systolic dysfunction.

Secondly, other non-classical effects of PTH have been described on the central and peripheral nervous system. PTH increases the N-like calcium channels in isolated neurones, a direct effect of the hormone. Rat studies demonstrate increased calcium uptake in striatum cells, decreased tissue dopamine content in rat hypothalamus, increased neuroprotection around the ganglial neurones and increased apoptosis in rat PC12 cells at high concentration. So PTH affects cells that derive from the nervous system (Wang 1993, Hang 1990, Harvey 1993).

In primary hyperparathyroidism a number of changes in nerve cell function of the patient give rise to psychiatric and cognitive disturbances. There are mild personality changes, nervousness, severe depression, obsessive compulsive behaviours and paranoia. All the symptoms appear to improve after parathyroidectomy, and the severity of psychiatric symptoms is correlated to the increase in serum calcium. Severe psychiatric symptoms occur frequently in elderly patients, and depression is not improved by classical antidepressants. A liberal approach regarding surgical treatment should be taken into consideration even in elderly patients.

What happens in parathyroid disorders is a Pandora's box of neurological manifestations. Sometimes these can be the first presentation: neurological symptoms include neuromuscular irritability, laryngospasm, muscle cramps, dysphagia, dysarthria, tetany, chorea, seizures, oculogyric crisis. And mental manifestations include anxiety, depression, hallucinations, confusion, psychosis and bipolar affective disorders.

Third, PTH has been related to malignancy. PTH R1 is expressed in gastric, breast, prostate, thyroid and colorectal cancers and in osteosarcoma. PTH promotes the growth and invasiveness of prostate cancer cells in bone. PTH induces osteoblast proliferation and osteosarcoma cell migration. It also induces intestinal cancer cells. PTH receptor 1 in breast cancer cells shows higher affinity for PTHrP while in osteosarcoma the affinity is higher for PTH. Hyperparathyroidism is rarely due to parathyroid cancer but it is associated with a small but definite risk of developing malignancies that persists even after parathyroidectomy. Is there a common aetiological factor between hyperparathyroidism and the number of malignancies? Skin cancer, thyroid cancer and breast cancer appear to be much more frequent in hyperparathyroid patients than in the general population.

Is there a connection between hypoPT and cancer? The risk of malignancy in the large analyses from a registry in Denmark (Underbjerg 2014) seemed not to differ except for G-I cancer. There seems to be a much lower risk of G-I cancer in these patients.

Key Learning Points:

- **The system of PTH, PTH receptors and receptorsome is very complex.**
- **Cardiovascular, metabolic, nervous system and cancer risks have not been addressed in practice guidelines**
- **In the future, more attention should be paid to these non-classical symptoms**

Cardiac Manifestations

Speaker: Prof. Jens Bollerslev *(Norway)*

PTH has been linked to the cardiovasculature and to cardiovascular disease. Chronic HypoPT in adults is in principle a two-hormone disorder affecting calcium homeostasis. Patients lack PTH but they are also deficient in the step that activates 1,25 dihydroxyvitmain D. PTH is metabolically active beyond regulating calcium homeostasis. Hagstrom (2019) looked looked into the association between PTH and cardiovascular mortality in a large population of elderly men in the region of Uppsala. The median observation time was almost 10 years. Throughout the entire spectrum of PTH levels, the hormone level was associated with cardiovascular mortality. This association, moreover, was not linked to disorders of PTH function such as hypo or hyperparathyroidism.

Furthermore, we know from large epidemiological studies that the calcium level by itself is also closely linked to cardiovascular disease. When it comes to gene expression, the PTHR1 receptor is mainly expressed in the kidney and at much lower levels in other tissues, and even at very low levels in cardiac myocytes. The PTHR2 receptor is mainly expressed in the brain, pancreas and endothelial cells throughout the body. Only the type 2 receptor is expressed positively in the vasculature. PTH and calcium levels go hand in hand as risk factors for various outcomes, including cardiovascular morbidity and mortality.
In normal physiology calcium is tightly regulated within very narrow biological variation whereas in HypoPT calcium fluctuates secondary to the disease itself as well as to variability in the medications.

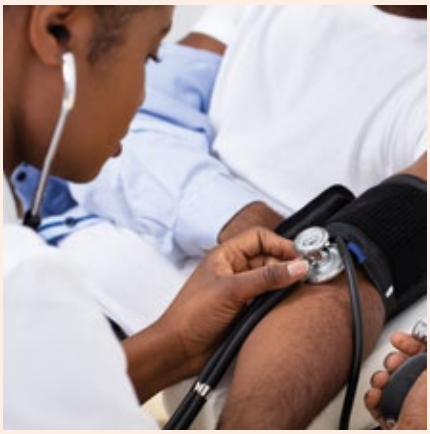
Replacement therapy with rhPTH (1-84) has become a reality for the treatment of HypoPT. Clarke (2014) looked at PTH levels over time after a single injection of 50 or 100 mcg of PTH. There was a sharp rise of PTH after injection, levelling off in about 3 hours to a lower level and was undectectable after about 12 hours.

Data on cardiovascular disease
Underbjerg (2013) published data on a huge cohort of patients with post-surgical HypoPT who were compared with matched controls. There were a total of 680 patients and three times that number of controls. Among patients with post-surgical HypoPT, in the unadjusted model, an increase in the number of patients with ischaemic heart disease and cardiovascular disease was observed. But mortality was not changed.

Then it was recognised that some of the patients had cardiovascular disease prior to their surgery. When the figures were adjusted for prior cardiovascular disease and diabetes, or prior diabetes and renal disease, the two significant findings disappeared. The point is here that the risk for cardiovascular disease was increased in these patients prior to the primary surgery which led to HypoPT. It could not be specifically attributed to HypoPT itself.

Another study, also from Denmark (Underbjerg 2015) focused on the risk of cardiovascular disease in non-surgical chronic HypoPT. 180 patients were identified, half of whom did not have a known aetiology. In the post-surgical cohort just described the observation time was around 10 years but this group has a much more prolonged observation time of almost 50 years. In patients with non-surgical HypoPT the increase in mortality was of borderline significancey. Cataract was significantly increased, renal complications were increased compared to the background population and different cardiovascular diseases, and higher in the patients with chronic HypoPT compared to the background population.

The non-surgical patients have a significantly increased hazard ratio (1.98) for any cardiovascular disease and for ischaemic heart disease (2.01) whereas the post-surgical do not have that.



Underbjerg (2018) recently published a case control study of 431 patients looking at complications in HypoPT. The population was divided into tertiles and then the tertiles were compared. Overall mortality was increased in patients with high phosphate levels and high CPP. Disease duration was associated with CVD and overall mortality. Lower than normal calcium levels were associated with increased risk of CVD, and mortality and risk of complications increased with the number of hypercalcaemic episodes.

In conclusion, PTH has actions beyond its role as a regulator of calcium homeostasis. Calcium by itself is directly coupled to atherosclerosis and ischaemic heart disease. Cardiovascular disease is increased in non-surgical HypoPT and is associated with disease duration also in post-surgical HypoPT.

Key Learning Points:

- **Receptors for PTH are found in the vasculature and heart**
- **In non-surgical hypoparathyroidism the risk for any CVD and ischaemic heart disease is doubled**

Renal function and the ENDORSE study

Speaker: Prof. Andrea Giustina *(Italy)*

HypoPT is an endocrine disease that has a big impact. In Italy alone more than 40,000 total thyroidectomies are performed every year and in at least 3-6% of cases persistent HypoPT is a result. Renal failure is about 3 times more common in post-surgical HypoPT than in the general population. HypoPT is the only endocrine disease which is not routinely substituted with the lacking hormone but using calcium and vitamin D. The patient cannot always be controlled well with this so-called standard therapy and renal manifestations, particularly hypercalciuria and nephrocalcinosis, are very frequent. They are generally related to the use of large doses of active vitamin D like calcitriol but the causes of decreased renal function in patients with HypoPT and calcium and vitamin D are multiple. The use of drugs like active vitamin D generates more risk sometimes than benefit.

Many endocrine regulators of renal function can have some relationship with PTH. Fibroblast growth factor (FGF)-23 is the most important phosphaturic hormone. HypoPT patients often have increased FGF-23 and this is something that led some authors to hypothesise a potential interplay of PTH with FGF-23 in regulating phosphaturia. The RAAS is very important in regulating the vasculature at the renal level, body fluids and mineral metabolism, particularly sodium metabolism (Saki 2020). However, little is known concerning the RAAS and PTH. Through vitamin D PTH can really impact on the RAAS but also potentially the RAAS may impact on PTH secretion (Zheug 2020). Very few data are available on the various markers of this system in HypoPT patients. Vasopressin is another very important hormone for renal regulation, and particularly for water balance and also for sodium resorption, and as yet there are no data concerning vasopressin and HypoPT.

The GH/IGF-1 axis really has very important effects at the kidney level, for example with an antinatriuretic effect, with an action on retaining phosphate (Kamenicky 2014). In patients with excess GH renal hypertrophy is observed, and clearly there is significant sodium and water retention in these patients. It is possible to speculate that the GH/IGF-1 system can be impactful in patients with HypoPT. There are no data on this but there are some data on pseudo HypoPT and hyperPT.

To summarise the hormonal effects on renal handling of the main electrolytes, some hormones (FGF-23 and PTH) are phosphaturic though GH/IGF-1 are antiphosphaturic. PTH can be natriuretic whereas most of the others (vasopressin and GH/IGF-1) are antinatriutetic. The effect on calciuria and anticalciuria is very important and the balance is something to be kept in mind.

The ENDORSE study

This new ENDORSE study (Endocrine determinants of renal function in patients with hypoparathyroidism) is being carried out at the San Raffaele hospital, Milan. The working hypothesis of the study is that HypoPT may cause renal damage influencing multiple renal hormonal axes. The study is cross-sectional, including more than 100 patients with post-surgical HypoPT on conventional treatment. The primary end point of this study will be to evaluate the prevalence of renal insufficiency in this population, and the activities of PTH-related renally active hormones on HypoPT patients treated with calcium and vitamin D. Hormone levels will be compared among patients with normal and impaired renal function.

The patients included will have chronic and persistent post-surgical HypoPT treated with active vitamin D. Beside evaluation of renal function based on calculation of the eGFR and of electrolyte balance, patients will be submitted to an assay of FGF-23, serum renin and aldosterone, serum vasopressin and IGF-1. HypoPT patients treated with human PTH preserve eGFR over time whereas patients on conventional treatment often lose renal function. This complication may be specifically linked via an indirect effect on a renally active hormonal axis. So kidney protection could be predicted to be one of the major benefits of PTH treatment in HypoPT.

It is hoped that this study will lead to an advance in understanding of the relationship between HypoPT and renal function. Further, it might form the basis for better understanding of how treatment with PTH can have an advantage over standard treatment concerning renal effects.

Key Learning Points:

- **Renal side effects are frequent in hypoparathyroidism patients on standard treatment**
- **The ENDORSE study may lead to better understanding of the advantages of replacement therapy**

Hypercalciuria and hypercalcaemia in Hypoparathyroidism

Speaker: Prof. Pascal Houillier *(France)*

HypoPT has traditionally been associated with calcium-containing urolithiasis and renal impairment because of an increased calcium-phosphate product (Bollerslev 2015).

What are the facts? A systematic review of the medical literature up to November 2018 revealed only 13 studies of more than 10 adult patients with HypoPT addressing the issue of nephrolithiasis, nephrocalcinosis, chronic and acute kidney disease and electronic glomerular filtration rate values (eGFR) The prevalence and the nature of renal diseases in patients with HypoPT were examined, namely nephrolithiasis, nephrocalcinosis and renal insufficiency. There are no data on acute renal insufficiency in patients with HypoPT, however.

Nephrolithiasis and nephrocalcinosis describe calcification in the urinary tract or renal parenchyma respectively. They occur because of an imbalance between the promoters and inhibitors of mineralisation. The cross-sectional prevalence of nephrolithiasis and –calcinosis in patients with HypoPT is assessed in different ways in different studies and the results appear rather heterogeneous, therefore. The apparent prevalence ranges from 1-2% to more than 35%. Overall it appears to be higher than in the general population, at around 15%.

Physicians commonly used GFR values to determine whether chronic kidney disease (CKD) exists. A figure below 60 ml/min/1.73m2 usually means renal insufficiency. Other factors do have to be considered in order to determine whether CKD is present or not, particularly albuminuria (KDIGO 2013). The cross-sectional prevalence of CKD in adult patients with HypoPT has been studied in several studies. Again the results are heterogeneous between the studies but in most of them prevalence is over 10%, up to 40%. In the French Epi-Hypo cohort, which includes about 1,000 patients now, the results are similar, with a prevalence of CKD stage 3-5 of 26%.

A recently published study (Chen 2020) reports the course of GFR over time in patients with HypoPT treated by rhPTH (1-84), comparing the data to those from an historical cohort treated with conventional therapy. The eGFR does not change from year to year in patients treated with PTH but it declines significantly each year in the conventionally treated patients. It remains uncertain whether PTH treatment protects against renal insufficiency.

How can patients with HypoPT become hypercalciuric and hypercalcaemic? The answer actually is quite simple, they cannot. For any plasma calcium concentration the urinary calcium excretion in patients with HypoPT is higher than for normal individuals, reflecting the lack of effect of PTH on the distal tubule. At steady state urine calcium excretion equals net entry of calcium in extracellular fluid. A patient with HypoPT does not have hypercalciuria or hypercalcaemia unless he visits a physician who treats him with calcium salts and active vitamin D. This may increase the flow of calcium into the ECF: the patient may become normocalcaemic, possibly hypercalcaemic and hypercalciuric.

In the general population the main risk for stone formation is hypercalciuria. In patients with HypoPT physician-induced hypercalciuria should also increase the risk of renal stones but this has not been demonstrated. Stone disease and risk are also affected by urine volume, oxalate excretion and citrate excretion. Those factors are almost never described in reports of patients with HypoPT, though they should be.

A study published in 2018 (Gafni 2012) reported the effect of teriparatide on urinary citrate excretion. Compared to pre-treatment values, urinary calcium went down on treatment but unexpectedly urinary citrate also went down. Both were completely reversible.

Hypercalciuria and hypercalcaemia may be able to affect renal function. For this, there would need to be calcium sensors in kidney cells. The most obvious candidate is the calcium-sensing receptor CaSR, which is expressed not only in the parathyroid glands but also in the kidney.

A study of the role of the CaSR in the thick ascending limb (Loupy 2012), using an antagonist, showed that the transmembrane permeability to calcium is increased when the CaSR is decreased.

There is evidence that distinct calcium sensing receptors exist in the kidney. Hypercalcaemia is known to induce polyuria and renal loss of sodium chloride in the urine. This effect is at least partially mediated by endothelin. An overexpression of the endothelin-1 gene has been observed in very specific tubular segments in patients treated with high doses of vitamin D. There is abundant literature to show that endothelin can be detrimental to renal function and play a role in the progression of chronic kidney disease.

The causative links between HypoPT and adverse renal outcomes have not been demonstrated but there are several potential targets or pathways to be investigated.

Key Learning Points:

- **Nephrocalcinosis or stones occur in about 15% of HypoPT patients**
- **Distinct calcium sensing receptors are found in the kidney**
- **Endothelin may play a role in chronic kidney disease**

Arterial stiffness and calcium or phosphate imbalance

Speaker: Prof. Lars Rejnmark *(Denmark)*

Epidemiological studies on risk of cardiovascular diseases in patients with HypoPT (Underbjerg 2013, 2015) show that non-surgical HypoPT, but not post-surgical HypoPT, is associated with an increased risk of CVD. A study from Scotland showed very similar results (Vadiveloo 2019). Bergenfelz (2020) showed that patients who had a history of cardiovascular diseases prior to acquiring HypoPT had an increased risk of adverse cardiovascular outcomes.

A clinical cohort study in patients with non-surgical HypoPT and pseudoHypoPT was recently carried out.(Underbjerg 2019). The aim was to identify indices of cardiovascular health in patients with HypoPT, measuring blood pressure and arterial stiffness in terms of pulse wave velocity (PWV). The study included 56 patients with non-surgical HypoPT and 30 patients with pseudoHypoPT.

Office blood pressure and heart rate did not differ between the two groups. Those with non-surgical HypoPT had a higher heart rate than those with pseudoHypoPT. This also applied when measurements were divided between measurements performed during the day and those measurements performed during the night. The results were not changed by restricting the analysis to those not being treated with an antihypertensive drug or after adjustment for differences in age.

The PWV was significantly increased in the non-surgical compared to the pseudoHypoPT patients but there were no differences in central measurements of blood pressure.

Pamuk (2020) compared 42 patients with chronic HypoPT, most of them post-surgical, to 60 healthy volunteers matched by age, sex and BMI. They measured BP and found that systolic and diastolic blood pressure were significantly higher in patients compared to the controls. Central measurements were also raised in patients compared to controls. However, this study did not show differences in heart rate. Also this study showed an increase in PWV in the patients with HypoPT compared to controls.

An inverse correlation between levels of serum calcium and measures of blood pressure as well as PWV; and a positive correlation between measurement of serum phosphorus and CPP and the PWV. Inverse associations were seen between the SBP and DBP and the PTH levels. In a multivariable regression analysis the only independent predictor of PWV was serum phosphorus levels.

The importance of biochemical regulation and risk for CVD was studied in 431 patients by Underbjerg (2018). Those patients with very low ionised calcium levels in the lowest tertile had significant increases in CVD risk, suggesting that calcium levels that are too low pose an increased risk of CVD. Those in the highest tertile also had an almost significantly increased risk of CVD, with a hazard ratio very similar to those with too low calcium levels. The study did not find an effect of phosphate levels or CPP but an increased number of hypercalcaemic episodes as well as an increased duration of disease were associated with an increased risk of CVD.

Two studies from India were presented next. A cross-sectional study compared 30 patients with non-surgical HypoPT with 30 controls, measuring intima-media thickness (IMT) (Meena 2015). Patients had higher IMT than the controls at the carotid, aorta and renal arteries. The non-surgical patients had significantly lower serum calcium levels and significantly higher phosphate levels but there was no correlation between these measures and the findings on IMT.

The same group produced another paper on coronary artery calcium scores in 30 patients with idiopathic HypoPT and 40 controls (Agarwal 2015). Serum calcium levels were much lower and phosphate levels were significantly higher in patients with non-surgical HypoPT compared to controls. Patients with non-surgical HypoPT had an increased prevalence of coronary artery calcifications. There were no correlations found between these calcifications and serum levels of phosphate or CPP, although these calcifications correlated inversely with age and serum calcium levels.

We are presently performing a study on patients with both post-surgical and non-surgical HypoPT is ongoing using high-resolution peripheral quantitative computed tomography (pQCT) scans. These are actually able to identify calcifications in the arteries of the lower leg. Studying 72 patients with HypoPT, 17% had calcifications in the lower leg whereas only 3% of controls were found to have calcifications in the lower leg. The frequency was similar in non-surgical and post-surgical patients. It was more frequent in men and it was associated with higher age and higher serum calcium levels and with lower Estimated glomerular filtration rate (Egfr) values.

In conclusion, several lines of evidence suggest that HypoPT, both post-surgical and non-surgical, has adverse effects on the cardiovascular system.

Key Learning Points:

- **Studies suggest associations between hypoparathyroidism and increased PWV and IMT**
- **An increased coronary artery calcium score and arterial calcifications in the lower leg may also be seen**

Impaired glucose metabolism and diabetes in Hypoparathyroidism patients

Speaker: Dr. Nicola Napoli *(Italy)*

It has been suggested that glucose metabolism and diabetes are important in patients with HypoPT. Through its effects on bone, PTH increases osteocalcin. In turn, osteocalcin may improve insulin secretion, beta cell proliferation, muscle insulin sensitivity and eventually testosterone production. PTH first increases osteocalcin followed by an increase in bone resorption markers like n-telopeptide.

In 2007 the Karsenty group (Wei 2015) suggested the hypothesis that osteocalcin is not just a bone protein but may also increase insulin expression, insulin secretion and beta cell proliferation, presenting the idea that bone and energy metabolism are interconnected. Carboxylated osteocalcin promotes calcium binding in the skeleton, identified as a component of the bone extracellular matrix where it binds with hydroxyapatite. Undercarboxylated osteocalcin may also have metabolic actions.

Mice lacking the osteocalcin gene have higher glucose and lower insulin levels (Lee 2017), (Feron 2010). When osteocalcin is injected into these mice, improvements in glucose and insulin levels are observed.

Pittas (2009), looked at the association between serum osteocalcin and markers of the metabolic phenotype in human subjects. He found that subjects in the lowest total osteocalcin tertile had higher plasma glucose compared to the second tertile and higher HOMA-IR, higher BMI, higher CRP, higher IL-6, more body fat and body fat percentage of total mass compared to the second tertile.

A secondary analysis of the PaTH study (Schafer 2011) examined postmenopausal women treated with rhPTH (1-84). The study found a steep increase in undercarboxylated osteocalcin in women treated with PTH. The increase in undercarboxylated osteocalcin was associated with lower body weight, lower fat mass and lower adiponectin.

The Diaz-Lopez study (2013) included patients at high risk of cardiovascular disease. The authors stratified patients according to tertiles of osteocalcin. Patients belonging to the lowest tertile of osteocalcin had a higher risk of developing diabetes compared to the second and third tertiles. There was a very significant effect in terms of prediction of type 2 diabetes in subjects with the lowest levels of osteocalcin.

An Italian study compared patients treated with rhPTH (1-84) to a group of subjects treated with calcium and vitamin D (D'Amelio 2015). These were elderly people usually seen in an osteoporosis clinic in Turin. A few weeks after the first PTH injection there was an increase in osteocalcin and an increase in undercarboxylated osteocalcin. But there was also a significant reduction in fasting plasma glucose in patients treated with PTH.

A study from Aarhus in Denmark specifically looked at patients with HypoPT treated with PTH or placebo (Harslof 2015). The findings from this study are important because they confirm the effect of PTH on improving body weight and total body fat mass in patients with HypoPT.

PTH may have an effect on bone anabolism through inhibition of SOST in osteocytes. SOST is a very important gene producing sclerostin, and sclerostin is the main inhibitor of bone formation. Data from Gennari (2012) implied the importance of sclerostin in type 2 diabetes patients, and Napoli's group (2018) confirmed these data, showing that patients with type 2 diabetes and also with LADA (latent autoimmune diabetes in adults) had higher levels of sclerostin compared to non-diabetic controls. The main determinant is the presence of metabolic syndrome, which may play a very important role in increasing sclerostin levels. Further, a study by Chen (Unpublished) proved that patients with HypoPT have a higher risk of developing diabetes.

Osteocalcin may work also through an effect on muscle, a very important organ for insulin sensitivity. Some authors have found an effect of osteocalcin on muscle, improving insulin sensitivity, through IL-6 and also reducing glucose output from the liver and improving the production of fatty acids from adipose tissue. The working hypothesis is that PTH replacement may improve glucose metabolism, inhibiting sclerostin, improving undercarboxylated osteocalcin but also improving insulin sensitivity throughout the muscle.

In conclusion, PTH treatment may produce a significant increase in osteocalcin leading to a reduction in body weight, a reduction in fat mass, an improvement in adiponectin and a reduction in glucose levels. Diabetes incidence might be improved by PTH treatment. Further studies are needed to understand the role of sclerostin suppression by PTH on glucose metabolism.

Key Learning Points:

- **Bone and energy metabolism may be connected**
- **PTH treatment may lead to increased levels of osteocalcin**

Cognitive function (brain fog)

Speaker: Prof. Leif Østergaard *(Denmark)*

There are prominent neuropsychological symptoms in patients with HypoPT. Astor (2016) found clinical anxiety in 38% of patients and clinical depression in 25%. Underbjerg (2014) found a higher risk of depression and bipolar disorder in their study. Also there are more subtle and more hard to quantify symptoms, so-called brain fog.

Basal ganglia ossifications are seen in as many as 75% of HypoPT patients by x-ray (Goswami 2012). Strange pericapillary deposits of material have also been observed in these patients at autopsy. Pericytes are the main cells that can actually produce or generate calcifications in the central nervous system. They are embedded in the basement membrane of the capillaries (Kida 2011). They are critical for maintaining the integrity of these capillaries. They control capillary diameter in the proximal part of the capillary bed. They control blood brain permeability and express PTH1 receptors. They constrict along the capillary if they are exposed to oxidative stress or toxic proteins.

The significance of capillary transit time is becomingly increasingly recognised. Extraction of oxygen depends on how capillary flow is distributed. There are two potential sources of tissue hypoxia: one is limited blood flow and the other is severely disturbed capillary flow that reduces the uptake of the oxygen.

Capillary transit time heterogeneity (CTH) is the standard deviation of these flows and transit times. Over a lifetime transit time heterogeneity increases more and more, and irreversibly so. In the beginning, they can be counteracted by increasing blood flow but eventually shunting occurs. Higher blood flow also means shorter

transit time. Adding a risk factor that destroys capillary function faster, as in Alzheimer's disease, means that this point is reached earlier. Similarly, the hypothesis is that if the patient loses signalling from pericytes because of lack of PTH then disturbed tissue oxygenation and blood flow will occur.

Typical scans of patients with HypoPT show some disticintive features: disturbed capilliary flow, large ventricles (indicative of neurodegeneration) and leakage of contrast agent. The hope is to correlate structural changes and pericyte changes with cognitive function.

Finally, oxygen levels are believed to be low in these patients, which could affect the amount of serotonin that can be produced. Low brain serotonin levels are associated with lower mood, anxiety and also susceptibility to depression. It would be interesting to know whether capillary dysfunction actually contributes to this susceptibility to depression.

Key Learning Points:

- **Hypoparathyroidism is associated with depression, anxiety and brain fog**
- **An interaction between PTH and cerebral pericytes is a plausible hypothesis to account for these findings**

Covid-19 and endocrine diseases

Speaker: Prof. Andrea Giustina *(Italy)*

The unprecedented effects of Covid-19 has devastated communities throughout the world. By 10 October 2020 there were 350,000 ascertained cases of Covid-19 in Italy; the mean age of patients who died was 80 years and mean number of co-morbidities was 3.4.

Covid-19 has an impact on the whole endocrine system. It affects the thyroid, parathyroid, adrenal glands and others (Marazuela 2020). The impact of diabetes and obesity on the severity of Covid has been reported widely.

The Covid Calcium, bone and Vitamin D study focused on the large cohort of those attending San Raffaele hospital, Milan in the first months of the pandemic, looking at their calcium metabolism and vitamin D and their bone. The first case report published in the literature concerning a case of severe hypocalcaemia in a patient with Covid-19 (Bossani 2020) raised interest in the study of calcium metabolism.

Among a large cohort of patients (531 patients) with Covid-19 who were admitted to the emergency department of San Raffaele (Di Filippo 2020) hypocalcaemia was found in almost 80%. Interestingly, hypocalcaemia correlated well with parameters of inflammation and predicted hospitalisation of the patient. Furthermore, hypocalcaemia was more common in patients hospitalised for Covid than those hospitalised for other reasons.

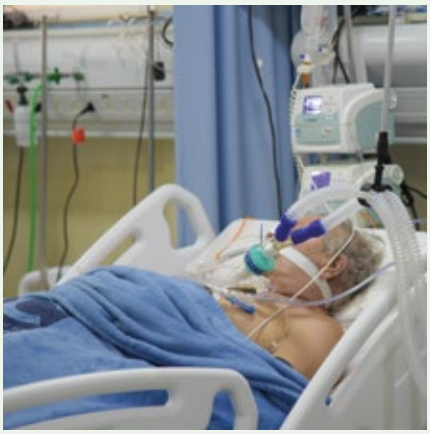
Vitamin D

Vitamin D supplementation is a potential preventive for acute respiratory tract infection. The distribution of hypovitaminosis D and Covid 19 is quite strikingly aligned in European countries. Obviously vitamin D can be important for Covid-19 for many reasons but particularly because it maybe able to modulate inflammatory cytokines and prevent the cytokine storm that is observed in the very severe cases of Covid-19.

D-Avolio (2020) published one of the first studies showing that low levels of vitamin D were correlated with a higher risk of having Covid-19 but also with disease severity. Among the few interventional studies, one from Spain studied hospitalised patients who received standard treatment for Covid-19 together with, or without, vitamin D. The authors observed that the severity of Covid-19 was much lower in the patients treated with vitamin D, than those who were not. It is very important to maintain vitamin D treatment in those that are already diagnosed with hypovitaminosis D. Treatment with vitamin D may be considered particularly in elderly patients with comorbidities who are confined at home.

Vertebral fractures

Professor Giustina discussed the prevalence of radiological thoracic vertebral fractures in patients hospitalised with Covid-19 (Di Filippo 2020). Many vertebral fractures are evident only by chest x-ray. Among patients with Covid-19 who had available a lateral projection X-ray, more than one third of patients had at least one vertebral fracture, making this co-morbidity one of the most frequent so far described in Covid-19. Vertebral fractures in Covid-19 are particularly important clinically because they predict the requirement of non-invasive mechanical ventilation, and also the mortality is doubled in patients with Covid who have fractures compared to those without fractures. Mortality is significantly higher in those with more severe fractures.



In conclusion, hypocalcaemia is an emerging strikingly frequent finding in patients with Covid-19. It may be related to the mechanism of viral infection and to poor biochemical status. It can be predictive of the severity of the disease and can be related to a negative impact on the outcome of the patient. Monitoring of calcium and its adequate supplementation are important in patients in whom hypocalcaemia is found. The finding that vertebral fractures are common in Covid-19 is important, because their associated respiratory problems may be correlated with clinical outcome. Professor Giustina recommended monitoring of calcium, vitamin D, and evaluation of AP and lateral chest X-rays in all patients with Covid-19.

Key Learning Points:

- **Hypocalcaemia is a frequent finding in Covid-19 patients**
- **Patients should be evaluated for vertebral fractures**

Hypoparathyroidism morbidity

Speaker: Dr. Tanya Sikjaer *(Denmark)*

The studies examining morbidity and mortality in HypoPT are very heterogeneous with regard to study populations, methods and collection of data. They include register-based studies and case-control studies, patient chart reviews and prescription databases.

The data on mortality are quite sparse and the results are not consistent. There is no difference in mortality compared to controls for non-surgical HypoPT according to results from Denmark (Underbjerg 2014) and Korea (Kim 2020), and for post-surgical in Danish and Scottish (Valdivelo 2018) cohorts. The only study to show an increased risk of dying in post-surgical HypoPT is the study by Almquist 2018).

Renal stones have been investigated in patients with post-surgical HypoPT by Mitchell (2012) and others with renal imaging and ICD codes. An increased risk of renal insufficiency has been shown in all studies, and renal disease was more common (Vadiveloo 2018).

Renal stones and renal insufficiency have also been investigated in non-surgical HypoPT patients. The overall renal disease was increased, as shown by Underbjerg (2014) and Kim (2020). In regard to stones, there was no increased risk in the Danish cohort but an increased risk of 2.13 in the Korean cohort. There was an increased risk between 3.44 and 6.01 for developing renal insufficiency.

The cardiac comorbidities examined in post-surgical HypoPT include arrhythmia, acute myocardial infarction and total CVD. There is no evidence of increased risk of arrhythmia in any of the studies although a high incidence has been noted. AMI was investigated in only one study and there was no increase in risk. The incidence of total CVD was not found to be higher than in controls in two studies once the results were adjusted although another study found an increased risk for cardiac events. Cardiovascular autonomic neuropathy has been shown to be highly increased in patients with HypoPT compared to controls, and this might represent a new parameter to investigate.

In non-surgical HypoPT patients, two studies showed an increased risk of arrhythmia, in contrast to post-surgical HypoPT. In regard to acute myocardial infarction (AMI), there was no difference between controls and non-surgical HypoPT; as regards total CVD there was no increased risk in the Korean study but there was an increased risk of 1.91 in the Danish study. One study found a longer QTc interval in 57% of patients. With regard to ischaemia, there was no increased risk in the Korean study but an increased risk of 2.01 in the Danish. Heart failure is a separate parameter in the Korean study, with an increased risk of 2.43.

Seizures in patients with non-surgical HypoPT have been investigated by Underbjerg (2014), Vadiveloo (2018) and Kim (2020). All showed an increased risk. Only two studies have been performed of seizures in post-surgical patients. Increased risk of hospital admission due to seizures is seen especially in patients with non-surgical HypoPT, and the risk varies from 1.63 to 10.05.

Neuropsychiatric diseases in patients with HypoPT have been investigated using questionnaires and ICD codes. There is a higher incidence of depression and bipolar disorder in both post-surgical and non-surgical HypoPT. The Korean study shows an increased risk of 1.82 in non-surgical. There is no difference in anxiety between controls and patients with HypoPT. A Norwegian study using validated questionnaires found that 38% of patients had anxiety. In patients with non-surgical HypoPT the risk of other neuropsychiatric diseases was 2.53.

Fractures have been investigated in patients with post-surgical HypoPT using ICD codes, but these might not detect vertebral fractures. Underbjerg investigated various anatomical sites for fractures but only the proximal humerus was significantly different from controls, with a lower fracture risk.

Among non-surgical patients, any fracture has been investigated using ICD codes and X-rays. In the proximal humerus there was an increased fracture risk of 2.81 in the Danish study but no difference in the larger Korean study. In regard to vertebral fractures, there was an increased risk by 2.27 in the Korean study but when investigated by X-ray there was a significantly higher incidence in non-surgical compared to controls. The fractures also occurred in patients with high BMD.

In post-surgical HypoPT there have only been studies of cataract using ICD codes. Valdivelo (2018) shows no increased risk. In non-surgical patients, all studies except the one by Vadiveloo showed an increased risk of cataracts between 1.9 and 4.21.

Two investigators have looked at infections. In surgical HypoPT Underbjerg (2014) found an increased risk of 1.42 of any infections but this was not found by Vadiveloo (2018). In regard to non-surgical, there was an increased risk at all sites in both studies. The risk of any infection ranged from 1.79 to 1.94 and the most common infections are UTIs.

In post-surgical HypoPT a study from Denmark showed no increase in any cancer but a reduction in G-I cancer. There is only one study in patients with non-surgical HypoPT, and it showed a lower malignancy risk of 0.44.

Key Learning Points:

- **Autonomic neuropathy could be clinically relevant**
- **The risk for infections needs further investigation**
- **Patients may have increased risk for vertebral fractures**

Hypoparathyroidism; Pregnancy and lactation

Speaker: Dr. Sigríður Björnsdóttir *(Sweden)*

A Swedish population-based cohort study, Bjornsdottir (unpublished), found the majority of patients with chronic HypoPT to be women. During pregnancy calcitriol levels increase, resulting in enhanced intestinal calcium absorption. Parathyroid hormone peptide related production by the placenta and breasts also increases in pregnancy. Interestingly, some women require higher doses of calcium and calcitriol during pregnancy compared with what they usually take but others require lower doses.

Close monitoring is important during pregnancy as high calcium in the mother may suppress fetal parathyroid gland development, and low calcium in the mother may result in secondary hyperparathyroidism in the fetus which can cause demineralisation of the fetal skeleton and intrauterine fractures.

There are limited data on pregnancy outcome in women with HypoPT and those are mainly in the form of case reports. Sweden has high quality population-based registers covering essentially all inpatient care and birth records. This study linked data from three national registries: the patient register (which includes both inpatients and outpatients), the prescribed drug register, which has collected data since July 2005, and the medical birth register which includes prospectively collected information since 1973.

The study included all women with a diagnosis of HypoPT during the period 1997 to 2017. The prescribed drug register was used to increase the diagnostic accuracy and only include women with chronic HypoPT: women were only included in the study if they had a diagnosis of HypoPT and also at least two dispensations of active vitamin D with or without calcium 13 to 24 months after the first entry of diagnosis of HypoPT in the patient register. Ten controls were randomly matched to every patient. All women with a diagnosis of kidney disease prior to or 12 months post diagnosis (and their controls) were excluded, as were all women that had fewer than two dispensations of active vitamin D in the last year of follow-up, and their controls.

The study enrolled 1,520 women with chronic HypoPT and 15,200 controls. Of those 1,520 women 97 women, or 6.4%, gave birth after the diagnosis of HypoPT. They gave birth to 139 singleton infants. And of the controls, 1,030 controls (6.8%) gave birth to 1,577 infants.

Three quarters of the women had post-surgical HypoPT and one quarter had non-surgical HypoPT. There was no significant difference in mean age at delivery between women with chronic HypoPT and controls. There were no differences observed in smoking, use of oral tobacco, or differences in family or working status between the two groups. There was no difference in calendar year of delivery between the groups. There were more women in the chronic HypoPT group with maternal diabetes compared to controls and there were also more women with chronic kidney disease, though the numbers were small.

Mean pregnancy length in women with chronic HypoPT was shorter (39.7 weeks) compared to controls (39.2 weeks). More pre-eclampsia (5.7%) was seen in the HypoPT women compared to controls (2.4%) but there was no difference in eclampsia. There were no differences in Caesarean section between the groups. Infants born to mothers with HypoPT were shorter compared to controls, and the mean birth weight was also significantly lower. After adjustment, HypoPT remained significantly predictive of low birth weight

but not low birth length. There was no difference in head circumference. There was no difference between the groups with respect to infant sex, Apgar scores, congenital malformations or stillbirths.

In conclusion, there was no difference in parity. Women with chronic HypoPT had shorter pregnancy length, they more often had pre-eclampsia, and infants born to mothers with chronic HypoPT had lower birth weight. There was no difference in birth length, Apgar score, congenital malformations or stillbirth. So the majority of women with chronic HypoPT in Sweden had normal pregnancy outcomes and the overall risks are low. The observed shorter pregnancy lengths could be the result of more frequent pre-eclampsia or uterine irritability caused by hypocalcaemia. Lower birth weight could be the result of shorter pregnancy duration.

Key Learning Points:

- **The overall risk of adverse pregnancy outcomes is low in women with hypoparathyroidism**
- **Pregnancy duration is slightly shorter in women with hypoparathyroidism**

Rapid Clinical Summaries

Symptoms, disease burden, quality of life of hypoparathyroidism patients, and impact on their caregivers

Speaker: Prof. Heide Siggelkow *(Germany)*

Trials investigating quality of life can be placed into 4 categories. First, validated generic questionnaires using healthy controls. Second, trials using validated generic questionnaires and a reference population. Third, trials using a specific questionnaire for HypoPT patients, and fourth those using specific questionnaires for HypoPT patients and a reference population.

First the Sikjaer study (2014) using rhPTH (1-84) investigated the SF-36 and the WHO-5 wellbeing index survey at baseline. At baseline the physical component scores were different but there were no correlations between SF-36 score, BMI, age, duration of disease or aetiology of the disease. They concluded patients had significantly reduced QoL at baseline in comparison with norm-based scores.

A Norwegian study (Astor 2016) investigated quality of life using the SF-36 and the hospital anxiety and depression scale (HADS) score. The SF-36 and HADS score were significantly different to the normative population. The post-surgical patients scored worse than those with non-surgical HypoPT.

A study from Denmark (Underbjerg 2018) looked at QoL in patients with diabetes, CVD and depression compared to that in patients with non-surgical HypoPT. Spider diagrams from the SF-36 were used to display how the different patient groups compared. Also the impact of symptoms on daily life was investigated. Those HypoPT patients with moderate or severe complaints had problems with relationships, ability to work, sleep or exercise in 60-80% of cases. Of those with severe symptoms 4 out of 5 patients changed their employment status. The caregivers themselves were working at 79% of their full capacity compared to before, and 28% of the caregivers reported major impact on their relationship.

In the second trial category, the study from Arlt (2002) compared 25 female patients with HypoPT with the reference population. These are age-matched controls, females with subtotal thyroidectomy matched for time since surgery. Using different questionnaires, the global score was significantly different compared to the patients operated on only for thyroid disease.

Sikjaer (2016) compared 22 patients with post-surgical HypoPT with 22 patients operated on only for thyroid disease and 22 healthy controls. They used the SF-36 and the WHO-5 and also investigated muscle function. The physical components score was significantly lower in patients with HypoPT compared to those operated on only for thyroid disease but for mental components there was no difference between those operated on for thyroid only and those also with HypoPT.

What about the specific questionnaires? Last year there were 3 tools developed and published, the HypoPT symptom diary, the HPES symptom score and the HPQ28 questionnaire. The HPQ28 questionnaire was developed and compared in three groups—patients with post-surgical HypoPT, a group operated on for thyroid disease and a third reference group with primary hyperparathyroidism. Some domains or areas of complaints are clearly different between the HypoPT group and the other two groups.

Which parameters influence quality of life? Some possibilities are duration of disease, current medication, hormone replacement and education. For example the Wilde study (2020) had two reference populations. Serum calcium was correlated with neurovegetative symptoms, CPP was correlated with a number of items, and higher CPP values were correlated with more symptoms.

There are a number of studies looking at how quality of life is influenced by rhPTH (1-84) treatment. The first study from Sikjaer (2014) used rhPTH (1-84) 100 mcg in addition to the normal medication and looked at quality of life after 24 weeks. Interestingly, there was no influence on the mental or physical components score after 6 months using rhPTH (1-84).

The next study comes from the Bilezikian group (Tabacco 2019) after 8 years of therapy with rhPTH (1-84). They used 69 patients and the SF-36 for analysis. There was an increase in mental and physical component scores over 8 years compared to baseline. They compared the effect to the normative population at baseline and at 8 years. There are some domains which are not influenced between baseline and 8 years, and there are others like mental health or social functioning which are nearly normalised.

Data from the REPLACE study (Mannstadt 2013) were analysed at baseline and after 24 weeks. In the placebo group there were no differences between beginning and end SF-36 results, however when using rhPTH (1-84) there was a significant difference in some of the scores.

Finally, some data using the HPQ28 were demonstrated as a poster at the German congress of endocrinology in 2020. Ten patients with chronic post-surgical HypoPT were investigated. The duration of HypoPT was 15 years, and they had replacement medication for about 1 year. The HPQ28 was filled out before first treatment and then every time they came for a visit, with a mean of 8 times per patient. After 1 year an effect of rhPTH(1-84) on pain and cramps was still evident, and on neurovegetative symptoms, while there was no effect on depression and anxiety.

Key Learning Points:

- **Hypoparathyroidism patients have reduced QoL compared to healthy controls and reference populations**
- **Effects may vary with age and gender**
- **So far, underlying thyroid disease and duration of disease seem to have little effect**

Risk for infection and resultant hospitalization in patients with hypoprathyroidism

Speaker: Dr. Mary Anna Venneri and Prof. (Assoc) Andrea Isidori *(Italy)*

The story about PTH and immunity goes back a long way. The first evidence came in 1984 with demonstration of the PTH receptor on human lymphocytes. There are clinical data suggesting that high PTH could be important and there are a lot of data on the role of intracellular calcium, but the two aspects have always been considered separately.

A breakthrough in the research came from the study by Rejnmark and colleagues (Underbjerg 2014), who showed that patients with low PTH had an increased risk of infections. These patients can have an increased risk of urinary tract infections due to calciuria but interestingly the increased risk of infection was still present when taking out UTIs. In order to prove that there is an immune defect, it needs to be determined whether patients have an increased susceptibility to develop frequent infections. Patients with HypoPT clearly had higher numbers of infections (more than 5 or 6). Do biochemical parameters have an influence? Very surprisingly, they showed that calcium and the CPP were not associated with the increased risk. Also, very high vitamin D doses were associated with protection against infection.

These studies, being registry based, have some limitations. The prospective study, EMPATHY (Puliani 2021), did full immune profiling of patients with HypoPT, looking not only at the circulating cells but also at the expression of PTH on the surface of these cells. The baseline characteristics of the two groups of subjects were well matched apart from a slightly higher BMI in the HypoPT patients

Looking at the immune cell profile of these patients, a combination of specific markers was used to characterise the profile of monocytes in peripheral blood in patients and controls. The analysis showed that patients with HypoPT had roughly half the population of circulating monocytes compared to controls. Integrated analysis was used to study the relative proportions of monocyte subsets. Patients and controls had comparable percentages of classical inflammatory and non-classical monocytes but the proportions of intermediate monocytes in HypoPT were significantly higher. These are of clinical interest because they are expanded in many inflammatory conditions, including sarcoidosis. Increases in intermediate monocytes are associated with chronic kidney disease and cardiovascular events in patients undergoing dialysis, and they could be involved in the cardiovascular risk of patients with HypoPT.

Total T lymphocyte counts did not differ significantly between the groups, however patients with HypoPT had decreased percentage of CD4+ T helper lymphocytes compared to controls. This could be related to impaired monocyte activation. The number of NK cells was significantly higher in patients with HypoPT compared to controls.

Given the role of calcium as second messenger in the immune response, the study examined the ratio of calcium-related gene expression. Expression of the main components of calcium signalling did not reveal any differences between patients and controls. Interestingly though, patients with HypoPT had significantly lower levels of GM-CSF and TNF alpha. In addition, TNF alpha was decreased in serum of patients. Of note, GM-CSF affects cell development, maturation and survival and is increased in several inflammatory conditions and cancer. The relative reduction in TNF alpha synthesis might also be the reduction in defence against infectious disease.

The PTH receptor was expressed on the plasma membrane of all lineages of patients and controls but the percentage of cells positive for PTH receptor was lower in patients. However, the intensity of expression was higher in patients in most monocyte subsets, possibly as compensation for lower circulating levels of PTH.

Pooling all normal and HypoPT patients together, there is a clear correlation between the changes in total monocytes and PTH level. The same correlation can be seen in terms of ionised calcium or inversely with phosphate. In order to fully address the real question, it needs to be proved that these changes are reversible by replacing PTH. Are immune alterations due to electrolyte imbalance or to PTH, and are they reversible? The EMPATHY 2.0 trial aims to prove whether a normal immune profile can be restored in HypoPT patients.

Key Learning Points:

- **The EMPATHY trial has demonstrated changes in monocytes, lymphocytes and NK cells**
- **These findings help to explain the increased risk of infection in hypoparathyroidism**

Clinical case: Calcification

Speaker: Prof. Markus Ketteler *(Germany)*

A patient case history of a female 67-year-old secretary with a long medical history was presented to illustrate nephrolithiasis and calcification in general in HypoPT. She developed HypoPT following subtotal thyroidectomy with accidental removal and/or damage of the parathyroid glands in 1973.

Her first bout of renal colic occurred in 1991 and she had 3 episodes of this before she was seen in the outpatient clinic in 2012. She had significant hyperphosphatemia, arterial hypertension, back pain, chronic pain, restless legs syndrome and depressive mood swings. In 2012 her medication was calcitriol 0.5 mcg twice a day, calcium carbonate 500mg 8 tablets a day in total, a phosphate binder containing aluminium (although that was paused before the outpatient appointment), L-thyroxine 125 mcg per day, a combination of irbesartan and HCTZ for hypertension, and painkillers on demand for her back pains. She also was given calcium tablets to take on demand if she was getting symptomatic.

She was referred to the nephrology clinic in 2012 for two reasons. First, she had a painful extra-articular soft tissue calcification next to her left elbow, and second, she had intermittent right-sided flank pain which was thought to be possibly another bout of renal colic. Her lab values included calcium 2.46 mmol/L, a high phosphate of 2.05 mmol/L, her PTH was suppressed, the calculated GFR was 66 ml/min, and she had a low 25-OH vitamin D level. On ultrasound the ureter was not dilated; she had suspected small nephrocalcinotic deposits in both renal pelvic areas but she had no signs of stone disease at that time. She was well mineralised.

So concerning the intermittent flank pain, PTH is a substance that is needed for reabsorption of calcium and magnesium by the kidneys. It is involved in inhibiting phosphate reabsorption but therapy with active vitamin D compounds leads to phosphaturia and so the composition of the urine changes. The building of vitamin 25 into active 1,25-OH2 vitamin D of course is stimulated by PTH.

Extra-articular soft tissue calcifications can be painful and can inhibit mobility. The other type of soft tissue or extraosseous deposition that concern physicians, especially in patients with hyperphosphataemia, is vascular calcification not least in the coronary arteries.

A few changes were made to her medication. Since the calcium of 2.46 mmol/L was high and the extraosseous calcifications suggested overtreatment, the active vitamin D was lowered. In addition she was started on a calcium magnesium binder instead of a pure calcium binder to control her phosphate. The thyroxine dose was lowered and cholecalciferol was added in order to get her native vitamin D levels into the recommended range. With all these measures, the calcium was lowered (possibly too far) but the patient was completely asymptomatic. A near normal phosphate level was obtained with these changes in medication.

The phosphate first went down, but then came back up again. This was a surprise so the patient was asked to come back to the outpatient clinic. A nutritional history was taken, with particular emphasis on her recent dietary habits. She said that her favourite food was pan-fried potatoes, not an obvious source of phosphate. However, on further questioning it came out that she was not using fresh potatoes but she was using store cupboard packaged potatoes that are put straight from the packet into the pan. This particular kind contains a lot of phosphate additives. These are phosphate salts that increase the usual shelf life of the food and add some taste to the food. But these phosphate salts have the capacity to be absorbed in the intestinal tract up to 100%, versus natural phosphate sources which are only absorbed in the range of 20-60%. So these phosphate additives were the culprit in this patient's case. She agreed to switch to fresh potatoes, and this formidable intervention led to normal phosphate levels within 2-3 weeks. Patients with HypoPT are at increased risk of CKD because the phosphate is not sufficiently excreted and if it is over the recommended levels for a long time such calcifications may really occur.

The case illustrates two types of unwanted calcifications, nephrocalcinosis plus soft tissue calcifications, which in this case was probably mostly triggered by the hyperphosphataemia but also perhaps by overcorrection of calcium.

Key Learning Points:

- **Kidney stones and extra-articular calcification may occur in hypoparathyroidism**
- **Phosphate additives in food can be 100% absorbed**

Clinical Case: Diabetes

Speaker: Dr. Nicola Napoli *(Italy)*

A clinical case of a 64-year-old Caucasian woman with post-surgical chronic HypoPT and diabetes was presented. She developed HypoPT after thyroidectomy in March 2018 for a papillary thyroid carcinoma. In 2016 she was also diagnosed with type 2 diabetes, and she had good glycaemic control with an HbA1c range between 6.5 and 7%. Her family history was negative for diabetes. She was a former smoker but not an alcohol abuser. Her estimated calcium intake was 800mg per day. Her medications included L-thyroxine 100 mcg 3 times a week and 1.25 mcg 4 times a week, calcitriol 0.5 mcg per day, calcium carbonate 1g 3 times a day and metformin for diabetes 850mg three times a day.

Before starting the patient on rhPTH (1-84) her glucose control was analysed. The patient was asked to collect several measurements of her capillary glucose at home. She reported fasting glucose in the morning between 135 and 145 mg/dL, a little bit lower at lunchtime and before dinner. Postprandial glucose was always above 150 mg/dL but still lower than 200 mg/dL. Her physical examination included a bodyweight of 78 kg; she was 165 cm tall with a BMI of 28.6 kg/m2. Chvostek's and Trousseau's signs were negative.

She complained of muscle cramps and tingling three times a week. Lab results showed an HbA1c of 6.4% (reasonable for her age), calcium corrected for albumin was 8.1 mg/dL, phosphate was 4.7 mg/dL, creatinine 0.7 mg/dL, eGFR 92 ml/min, cholesterol acceptable, 24-hour urinary calcium was 380 mg and her TSH was 0.8 mU/L.

In January 2020 she was started on rhPTH (1-84) at a dosage of 50 mcg/day, and this dose was increased to 75 mcg/day in March 2020. When she came back to the clinic 6 months after starting rhPTH (1-84) treatment, she was still taking calcium carbonate and calcitriol. Her calcitriol dosage was at that time reduced to 0.25 mcg/day. L-thyroxine and metformin were unchanged from baseline. The lab results in June 2020 showed that she had an improved HbA1c, serum calcium was still 8.7 mg/dL, phosphate 3.7 mg/dL, creatinine 0.8 mg/dL, eGFR 78 ml/min, vitamin D was 42 nmol/L and urinary calcium was 280 mg/24 hours. Looking at glucose control, the values before breakfast were all below 100 mg/dL. Also the values after breakfast were under 140 mg/dL so all glucose values were in the normal range. It was therefore decided to reduce the dosage of metformin and to give it just twice a day, at lunchtime and dinnertime.

Nine months from beginning treatment with rhPTH (1-84) the patient came back to the clinic. She was still on rhPTH (1-84) 75 mcg/day, calcium carbonate was still 800 mg and all the other medication dosages were as before. Lab results showed a further improvement: HbA1c was 6.1% now, with a corrected calcium of 8.9 mg/dL and a phosphate of 3.4 mg/dL. Glucose control was still satisfactory, with values before breakfast and lunch mostly within the normal range and levels after breakfast and dinner below 140 mg/dL. There was a slight increase in postprandial glucose after dinner but the values were satisfactory for a diabetic patient of that age.

So this patient is diabetic with HypoPT. With rhPTH (1-84) treatment it was possible to obtain better glucose control and lower HbA1c and to reduce the dose of metformin.

Key Learning Points:

- **Treatment with rhPTH (1-84) can improve glucose control in hypoparathyroidism patients with diabetes**

Hormonal therapy

Speaker: Prof. John Bilezikian *(USA)*

The clinical features of HypoPT include neuromuscular irritability, impaired quality of life, renal and extraskeletal calcifications and skeletal alterations (Bilezikian 2020).

The conventional therapy of HypoPT focuses on calcium, vitamin D and at times thiazide diuretics. With calcium and active vitamin D it is usually possible to maintain the serum calcium but control can be difficult. Further, the deficiency in renal calcium handling is not corrected. Abnormalities in skeletal metabolism persist, and the quality of life is not improved.

Without PTH many individuals with HypoPT receive either too much calcium and vitamin D or too little. In both situations individuals with HypoPT are at risk for a series of complications over time.

Recombinant human (rh) PTH (1-84) has been available for the past 5 years. Teriparatide is the foreshortened fragment of the intact molecule and there is some experience with teriparatide (Winer 2010). The effective half-lives are different, PTH (1-84) having a longer effective half-life than PTH (1-34) and when teriparatide is used for HypoPT multiple daily injections are needed as opposed to single daily doses of PTH (1-84).

The REPLACE trial formed the basis for the registration of rhPTH (1-84) for HypoPT (Mannstadt 2013), (EMA 2017). The trial had a composite triple end point. At the end of 24 weeks it was the percentage of individuals who could be maintained with a greater than 50% reduction in oral calcium, a greater than 50% reduction in their active vitamin D, and albumin-corrected total serum calcium at less than the upper limits of normal. Of those who received rhPTH (1-84) 53% met that composite end point, versus almost nobody who was treated with placebo.

There are now long-term data out to 6 years in the RACE study and other data which extend even longer than that. With regard to the RACE study, patients over 5 years had a 60% reduction in their oral calcium needs and an 80% reduction in their calcitriol needs. In addition, over a 6-year period a majority of patients were able to maintain that composite efficacy end point. Furthermore, there was a gradual but progressive reduction in urinary calcium excretion.

An observational trial from investigators at Columbia University was able to show clearly that rhPTH(1-84) stimulates bone metabolism. Over 8 years (Tay 2019) the serum calcium was maintained very consistently in the lower range of normal. In addition, the need for calcium supplements and calcitriol supplements fell gradually over that 8-year period. There was a gradual and progressive reduction in urinary calcium excretion over the same period of time.

A very important feature of HypoPT is the reduced quality of life, and this persists even in patients who are maintained on conventional calcium and vitamin D therapy. With rhPTH (1-84) treatment it was possible to show improvements in many domains of the SF-36 scale over 8 years.

With regards to skeletal disease in HypoPT there are markedly abnormal dynamic and structural elements. It is not known how these relate to bone strength and fracture incidence. After therapy with rhPTH (1-84) there are improved skeletal dynamics and bone density follows the expected effects of PTH in euparathyroid subjects. Microstructural elements are being studied, but the effect on fracture incidence is as yet unclear.

Current guidelines for the management of HypoPT come from Jens Bollerslev and the ESE (Bollerslev 2015), and from the international workshop that led to publication of management guidelines headed by Maria Luisa Brandi (Brandi 2016). The international workshop made six recommendations for use of rhPTH (1-84). The first indication for rhPTH (1-84) was the inadequate control of serum calcium. A second indication was

individuals who require more than 2.5g calcium or 1.5 mcg active vitamin D or more than 3 mcg of the 1 alpha analogue. The third and fourth indications relate to the kidney, covering patients with persistent hypercalciuria, kidney stones or stone risk, nephrocalcinosis and those whose creatinine clearance is less than 60 cc/min or who have hyperphosphatemia or whose calcium phosphate product is greater than 55 mg^2dL^2 (4.4$mmol^2$ L^2). The fifth indication relates to those with a G-I tract disorder that is often associated with malabsorption. Those individuals with reduced quality of life might also benefited from rhPTH (1-84).

In summary, studies with rhPTH (1-84) have established its efficacy in restoring mineral metabolism, in improving skeletal and renal indices as well as quality of life. Based on new data obtained over the past 5 years, many clinicians feel that it is timely to revisit the evidence-based guidelines for the management of HypoPT.

Key Learning Points:

- **Conventional therapy with calcium and active vitamin D provides adequate control in some patients**
- **Positive effects have been obtained using rhPTH (1-84)**

Is it time for a global hypoparathyroidism guideline?

Expert panel: Prof. John Bilezikian *(USA)*, **Prof. Maria Luisa Brandi** *(Italy)*, **Prof. Aliya Khan** *(Canada)*, **Prof. Michal Kršek** *(Czech Republic)*, **Dr. Polyzois Makras** *(Greece)*, **Prof. (Assoc) Andrea Isidori** *(Italy)*, **Prof (Assoc) Karin Amrein** *(Austria)*

A panel of experts chaired by Professor John Bilezikian, gave their personal insights on whether it was time to officially assimilate both the evaluation of patients with hypoparathryoidism, as well as its management.

Khan: There are advances in physicians' ability to treat HypoPT and intervene both acutely and on a chronic basis. In North America a panel of global experts has been assembled to review the literature, addressing all aspects of HypoPT, and to develop evidence-based recommendations.

Brandi: Guidelines usually need to be reviewed after a while. Though there is new collected information, does this translate into changes in management of these patients? Information on costs is very much needed, and care needs to be taken in defining future study populations.

Bilezikian: There are potential issues that are perhaps not investigated sufficiently when patients are first seen. (This might form part of future guidelines.) These include glucose tolerance, risk of infectious disease and dietary history.

Napoli: Data show that patients with HypoPT have an increased risk of developing diabetes, not only glucose intolerance but diabetes. PTH replacement therapy is of course not an antidiabetic medication but replacing PTH will decrease the risk of developing diabetes and improve glucose metabolism.

Isidori: There is now a lot more information to better define the patients with HypoPT who are at increased risk of infections. These patients have increased mortality due to infectious disease. Identifying higher risk patients is particularly helpful in those countries in which PTH replacement is not yet fully available.

Amrein: We need to better measure quality of life impairment. There are comparisons to measuring type 1 diabetes, given evaluation of HypoPT is very incomplete. Patients should be helped to improve their self-management skills; including self-measurement of calcium. This is more complicated to do than glucose control but it is needed. A visit once in 3 months certainly does not capture what everyday life is like for these patients.

Bilezikian: Doctors do not routinely worry about the skeleton in HypoPT - maybe they should pay much more attention to the vertebral compartment, for example, where there may actually be fractures.

Napoli: There should be a specific focus on cardiovascular risk because calcification of the vascular system is quite well known. These patients have been taking huge doses of calcium for many years; screening for vascular calcifications is easy now. Diabetes plus calcium deposition in the vascular system puts these patients at risk.

Bilezikian: There seems to be a logic in trying to identify those patients who are more likely to do well on PTH replacement therapy. How do you view recombinant human PTH or the other PTHs on the horizon? How will they fit into therapeutic paradigms?

Khan: It is important to consider when to offer PTH replacement, whether to offer it only when patients have failed conventional therapy or to people who are simply not doing well even though the biochemical profile looks great.

Amrein: The different PTHs on the horizon will make treatment of HypoPT more physiological. Again there is the analogy with type 1 diabetes.

Isidori: There are some patients who are at increased risk, and they will benefit most from physiological treatment.

Bilezikian: There are a number of different end points now in HypoPT, in many different systems. The guidelines would need to look beyond calcium levels

Bilezikian: Those doctors who have used rhPTH (1-84) have been impressed not just in terms of biochemical control but in quality of life.

Krsek: Logically replacement therapy with recombinant hormone is the future.

Makras: The complexity of the disease relates not just to medical problems but to financial issues. The elephant in the room is the cost, and this would not be a problem if it cost the same as thyroxine.

Bilezikian: The guidelines initiative will take into account the cost of treatment but also the financial burden of the disease itself. Patients going to the emergency room in crisis are a very expensive proposition as well.

Concluding remarks:

In summing up the meeting, Prof. Bilezikian expressed his belief that a lot of new knowledge has been developed about this rare disease. The conference presented new insights into renal involvement, the cardiovascular system, cognitive impairment as it may relate to cerebrovascular function, quality of life as it relates to hypoparathyroidism and the morbidity and mortality of hypoparathyroidism.

The future lies in understanding more about those pleiotropic effects of PTH under normal circumstances, and in the context of hypoparathyroidism how this replacement therapy can address some of the pervasive effects of PTH. Hopefully this can be addressed in a systematic, evidence-based way.

Interactive Faculty Q&A

Over the course of the event, participants took the opportunity to use digital interaction tools to pose questions to panelists and presenters.

SESSION 1

To > Prof. Gardella	Response
Would it be reasonable to assess TIP39 as a potential treatment for the adverse effects of HypoPT, especially the CNS effects on mood and cognition?	That is a very interesting idea that would have to be explored in animal model systems
How do 1-34 and 1-84 stimulate the PTH receptors in the brain. Is there a mechanism in place for them to cross the blood brain barrier?	It is an unexplored area. There is evidence for expression of PTHrP in the brain.

To > Prof (Assoc) Eriksen	Response
Do you expect differences in short-term symptom relief or long-term outcomes as risk of renal complications between PTH 1-34 and 1-84?	That remains to be seen.

To > Prof. Bilezikian	Response
How do the actions of PTHrP intersect with those of PTH in the classical organs?	That is a very good question and I don't think I can answer it!
Can you comment on the bone safety long term of hormone replacement in HypoPT?	For the cohort treated for up to 12 years with hrPTH (1-84) the data are extremely positive. No long-term negative effects have been seen. PTH is a very different ligand in rats and humans.
Is it possible to tailor a PTH molecule that could be organ- or tissue-specific?	This could be theoretically possible if there were differences not so much in the receptor but in the environment of the receptor from tissue to tissue.

To > Prof. Brandi	Response
Are you surprised that epidemiological studies have not demonstrated a higher risk of arrhythmia and sudden cardiac death in these patients?	It is true that the only population study in this area is the one from Rejnmark's group. Complications at the cardiac level and mortality are related to duration of disease. Registries will attempt to answer the question of how often cardiac symptoms are overlooked.
is there any evidence of receptor response to intermittent or continuous PTH 1-34 in humans?	We have experience of the intermittent use of PTH 1-34 in osteoporosis. In HypoPT patients may develop a lack of responsiveness after continuous exposure. Animal studies show that PTH is a very potent vasodilator, and it's a chronotrope and an inotrope. We need to make clinicians aware about this potential complication, and collect information from patients: we sometimes do not pay much attention to the CVS. We have been overlooking the cardiovascular complications and it is our responsibility to develop this area within the guidelines.

SESSION 2

To > Prof. Giustina and Prof. Houillier	Response
Would SGLT2 antagonists be suitable potentially for the treatment of patients with HypoPT?	The most important thing is to avoid development of renal insufficiency in these patients.
You talked about sclerostin in diabetes. Is sclerostin in addition a reasonable approach to the treatment of diabetes refractory to other therapies?	Antisclerostin therapy may be a good option for diabetic patients but we do not have any data yet in HypoPT.

SESSION 2 *CONTINUED*

To > Prof. Østergaard

The results you presented focus on evidence for a vascular hypothesis for brain fog in patients with HypoPT. Is there any evidence that direct effects of PTH on neurones may contribute to this disease complication?

Response

That is an excellent question and unfortunately I do not have a good answer for that.

What do you think about the reversibility of some of these abnormalities in patients who would be treated with PTH?

There is evidence that giving PTH can lead to reversal of symptoms.

To > Prof. Houillier

Do patients with CaSR mutation in the PARADIGHM registry have increased prevalence of nephrocalcinosis or nephrolithiasis?

Response

These patients are difficult to control. After some years they will develop renal insufficiency but it is extremely complex to know whether it is the disease itself, it is related to episodes of over-treatment or chronic hypercalciuria, or it is a mixture.

SESSION 3

To > Prof. Siggelkow

What is the practical use of these tools to assess quality of life in clinical practice?

Response

Patients fill out the questionnaire while they are waiting to see the doctor. It only takes 10 minutes and helps me to see the patient's situation straight away.

In studies looking at vertebral fractures patients had a lot of epileptic seizures and they were on a lot of medications for seizures and these have a bad effect on bones as well. Some of these fractures might come from the seizures.

To > Prof. Giustina

Is a high level of vitamin D associated with increased risk of infections other than Covid 19?

Response

There was a meta-analysis published a couple of years ago in the BMJ showing that people who are undergoing vitamin D supplementation were less at risk of developing respiratory infections. There is evidence that vitamin D levels and vitamin D supplementation may play a role in general in respiratory infections.

To > Prof. Ketteler

What specific dietary advice should be given to patients with HypoPT?

Response

The culprit in this case was the phosphate. Phosphates in food are of three kinds. The first one is based on vegetables, the second one is based on meat and the third one are these phosphate salts that are given to increase shelf life, taste and so on. For a patient with hyperphosphataemia it makes a difference to recommend the right sources of phosphate and also to look at fast food ingredients. For example, the cheese on a cheeseburger is not cheese, it is phosphate.

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SESSION 1

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