Diplomarbeit

Hypoparathyroidism:
a retrospective observational study – update 2021

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Graz, am 26.04.2022

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Graz, am 26.04.2022 *Simon Geiger eh.*

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Index

Abbreviations

ADH	Autosomal dominant hypocalcaemia
AHO	Albright's Hereditary Osteodystrophy
APS-1	Autoimmune Polyendocrine Syndrome I
BMI	Body mass index
Ca-SR	Calcium sensing receptor
CI	Confidence interval
CKD	Chronic kidney disease
COVID	Corona virus disease 2019
DGS	DiGeorge syndrome
eGFR	Estimated glomerular filtration rate
FGF-23	Fibroblast growth factor 23
Hb	Haemoglobin
HPT	Hypoparathyroidism
hPTH	Synthetic human parathormone
IMI	Institute of Medical Informatics
OPT	Osteoprotegerin
OR	Odds ratio
PA	Parathyroid autotransplantation
Pi	Inorganic phosphate
PHPT	Pseudohypoparathyroidism
PTH	Parathyroid hormone
PTH1R	PTH/PTHrP receptor type 1
PTHrP	Parathyroid hormone related peptide
RANKL	receptor activator of nuclear factor κ-B ligand
rhPTH	Recombinant human parathormone
SD	Standard deviation
SF-36	36-Item Short Form Health Survey
Vitamin D2	Ergocalciferol
Vitamin D3	Cholecalciferol
1,25OHD	1,25-dihydroxyvitamin D

25OHD	25-hydroxyvitamin D

Index of Figures

Index of Tables

Zusammenfassung

Einleitung

Der Hypoparathyreoidismus (HPT) ist eine seltene endokrine Erkrankung, bei der es durch unnatürlich niedrige Parathormon Spiegel zur einer Hypokalzämie kommt. Typische Symptome sind Parästhesien, Tetanien und Krämpfe. Unspezifische Symptome, wie Müdigkeit, Mattigkeit und Konzentrationsstörungen sind ebenso bekannt. Hypoparathyreoidismus wird in 75% der Fälle durch Operationen am Hals verursacht, zumeist Schilddrüsenoperationen.

Die konventionelle Therapie besteht aus oralem Kalzium und aktivem Vitamin D, seit 2017 ist eine Hormonersatztherapie mit rekombinanten humanen Parathormon (rhPTH (1-84)) zugelassen, falls die Therapieziele konventionell nicht erreicht werden können. Langzeitkomplikationen von chronischem HPT inkludieren renale, neuropsychiatrische und kardiovaskuläre Endpunkte.

Methoden

Dies ist eine retrospektive Beobachtungsstudie, bei der wir 191 PatientInnen mit chronischem HPT in der Steiermark identifizieren konnten und deren medizinische Daten von 2004 bis 2022 (MEDOCS) auswerteten.

Ergebnisse

70% aller PatientInnen waren weiblich und 30% waren männlich. Das durchschnittliche Alter war 62 Jahre und 82% hatten einen postoperativen HPT mit durchschnittlich 2,5 Jahren zwischen Operation und Diagnosestellung. Die meisten Operationen wurden aufgrund von Schilddrüsentumoren (30%) oder Struma (22%) durchgeführt. 90% der PatientInnen hatten Nebenerkrankungen. Am häufigsten waren kardiovaskuläre Erkrankungen (34%), gefolgt von renalen (27%) und neurologischen Erkrankungen (14%). PatientInnen, die mit rhPTH (1-84) behandelt wurden waren im Schnitt jünger ($p<0,001$) und hatten höhere Serum-Kalziumspiegel ($p<0,001$), niedrigere tägliche Kalzium Dosen ($p=0,027$) und niedrigere 1,25-hydroxyvitamin D Spiegel ($p<0.001$). 27% aller PatientInnen berichteten von Symptomen bei ihrer letzten Kontrolle. Die Anzahl an Krankenhausaufenthalten korrelierte mit der Anzahl an Komorbiditäten ($p=0,011$). 42% aller PatientInnen hatte im letzten Jahr eine mittlere eGFR unter 60 ml/min/1,7^2. Die mittlere Abnahme der eGFR pro Jahr betrug 1,5 ml/min/1,7^2. 30% der PatientInnen hatten eine Anämie bei ihrer letzten Kontrolle. Von 2011 bis 2021

waren im Schnitt jedes Jahr 44% der Kohorte anämisch. Anämien kamen häufiger vor bei PatientInnen mit chronischen Nierenerkrankungen Grad 3 oder schlechter (OR 3,3; p<0,001) und bei PatientInnen mit Komorbiditäten (p=0,024). 90% der Anämien waren normochrom/normozytär.

Conclusio

Der chronische Hypoparathyreoidismus ist eine komplexe Erkrankung und Langzeitfolgen sind bei vielen PatientInnen nach wie vor ein großes Problem. Auch eine Anämie ist häufig. Die Prävention und Behandlung dieser Langzeitfolgen werden in Zukunft höchstwahrscheinlich wichtige Forschungsbereiche darstellen, da diese eine große Krankheitslast und hohe Kosten mit sich bringt und viele der zugrundeliegenden Mechanismen noch unbekannt sind.

Abstract

Introduction

Hypoparathyroidism (HPT) is a rare endocrine disorder characterized by hypocalcaemia and inadequately low parathyroid hormone levels. Symptoms can be typical, such as paraesthesia, tetany, and spasms, but can also be unspecific, including fatigue, brain fog and concentration disorders. In 75% HPT is caused by anterior neck surgery, other aetiologies include autoimmune, genetic, and idiopathic causes.

Conventional therapy consists of oral calcium and active vitamin D supplementation and since 2017 hormone replacement therapy with recombinant human parathormone (rhPTH (1-84)) is available if therapy goals cannot be met conventionally. Long-term complications of chronic HPT include renal, neuropsychiatric and cardiovascular complications.

Methods

We identified 191 patients with chronic HPT in Styria and analysed their medical and laboratory data from 2004-2022 using MEDOCS.

Results

70% of all patients were female and 30% male. The mean age was 62 years and 82% had postsurgical HPT with a median time of 2.5 years from surgery to diagnosis. Most surgeries were performed because of thyroid cancer (30%) or goitre (22%). 90% had secondary diseases, the most prevalent being cardiovascular disease (34%), followed by renal (27%) and neurologic disease (14%). Patients receiving rhPTH (1-84) were younger ($p<0.001$), had lower serum calcium levels ($p<0.001$), lower daily oral calcium doses ($p=0.027$) and lower 1,25-hydroxyvitamin D levels ($p<0.001$). 27% of all patients mentioned symptoms at their last visit. The number of hospital visits correlated with the number of secondary diseases ($p=0.011$). 42% of all patients had a median eGFR below 60 ml/min/1.72 in their last year. The median eGFR lost across all patients per year was 1.5 ml/min/1.72. Anaemia was present in 30% of patients at their last visit. From 2011-2021 about 44% of patients were anaemic each year. Anaemia was more prevalent in patients with CKD grade 3 or worse (OR 3.3; $p<0.001$) and in patients with more comorbidities ($p=0.024$). 90% of anaemias were normocytic/normochromic.

Conclusion

Chronic hypoparathyroidism is a complex disease and long-term complications are highly relevant for many patients. These complications are linked to a lower quality of life. Anaemia is also highly prevalent. Management and prevention of these complications will most likely be an important field of future research, as they may cause a high burden of disease and costs and many of the mechanisms involved are still unknown.

Angaben von bereits erfolgten Veröffentlichungen

Eisenmangel bei Hypoparathyreoidismus – Koinzidenz oder häufige unterdiagnostizierte Komorbidität? Ein Fallbericht

Starchl C. · Geiger S. · Tmava-Berisha A.

ÖGKM Kongress 2020 Posterpräsentation (1. Preis)

Retrospective observational study: anemia in hypoparathyroidism – a common companion

S. Geiger · C. Starchl · G. Wünsch · A. Tmava · K. Amrein

ÖGKM Kongress 2021 Posterpräsentation (1. Preis)

Quiz: Schwere Knochen!?

S. Geiger · K. Amrein

Journal für klinische Endokrinologie und Stoffwechsel 2/2021

Hypoparathyreoidismus

S. Geiger · K. Amrein

Journal JATROS Diabetologie & Endokrinologie 5/2021

1. Introduction

1.1 Physiology

1.1.1 Calcium

The human body contains about one kilogram of calcium. More than 99% are stored in bone mineral as hydroxyapatite crystals, providing skeletal strength. The remaining calcium is located in the blood, extracellular and intracellular fluid (1–5). Calcium plays an essential role in bone formation, muscle contraction, intra- and extracellular signalling, nerve impulse transmission, haemostasis and hormone secretion (1,4). The average adult ingests about 1000mg of calcium per day with a net absorption of 100-200mg (4). Most of it (90%) is being absorbed in the small intestine via two pathways: paracellular and transcellular. Paracellular calcium uptake is a passive process of diffusion through the tight junctions between the intestinal epithelium cells along electric and concentration gradients, that prevails when calcium intake is adequate or high. Transcellular transport is an active, energy dependent mechanism largely mediated by 1,25-dihydroxyvitamin D (1,25OHD), which can be divided in three steps. First, apical calcium resorption, followed by binding to calbindin and transcellular movement and lastly basal excretion (6–8).

Total serum calcium concentrations range between 2.2 and 2.65 mmol/l, whereas 45% is bound to protein, especially albumin, and 10% is complexed to anions like citrate and phosphate (5). The remaining 45% (1.1 – 1.3 mmol/l) are free or ionized calcium – the biologically active fraction (1,2,9). Ionized calcium levels change with blood-pH increase or decrease, due to albumin binding more or less calcium (5,9).

Calcium metabolism and homeostasis is tightly regulated by a complex hormonal system involving parathormone (PTH), vitamin D, calcitonin and their receptors in the gut, kidney and bone (3,4). Ionized calcium levels are continuously measured by the calcium sensing receptor (CaSR), adjusting PTH secretion in a negative feedback loop (4).

Another major part of calcium metabolism is bone turnover – a constant remodelling process coordinated by hormones and growth factors (4).
The main pathways for calcium loss are through the skin, gut and kidney. The average human kidneys filter approximately 10g of calcium per day, whereas only 200mg are excreted. This reabsorption of 98% is taking place in the renal tubules as an active or passive process and is, in part, regulated by hormones and serum calcium levels (9,10). Maintaining calcium homeostasis is of utmost importance in numerous diseases and can be essential for treatment success.

1.1.2 Phosphate

Inorganic phosphate (Pi) is essential for various key biological processes like energy metabolism, cell signalling, membrane stabilization and pH-regulation, as well as being building blocks of DNA and RNA (1,11). The average adult body contains about 700g of Pi and, similar to calcium, 85% are bound in bone mineral as hydroxyapatite (1,5,11). Only 1% of Pi is located in the extracellular fluids, with serum levels between 0.84 and 1.45 mmol/l (5). Pi consumption on average is about 1000mg per day, with a net absorption of 65 to 90% (4,5). The two main pathways for intestinal Pi uptake are paracellular and transcellular. Paracellular transport is largely dependent on luminal Pi concentrations and is a passive process. Transcellular transport occurs through the sodium-phosphate type IIb cotransporters and is partly regulated by vitamin D (4). Pi balance is maintained by numerous endocrine factors, including PTH, vitamin D, fibroblast growth factor 23 (FGF-23) and its coreceptor α-klotho (11).
Circulating Pi, unlike calcium, is not bound to protein and therefore almost completely filtered at the glomerulus (4). Up to 85% are reabsorbed within the nephron, mostly in the proximal tubule. This active process is driven by higher extracellular sodium levels and depends on the basolateral sodium-potassium pump and apical sodium-phosphate type II cotransports. Renal Pi reuptake is influenced by several variables, like PTH and FGF-23, but also dietary phosphate intake (4,11). Additionally, calcium and Pi share a solubility product, leading to low free calcium levels when Pi is high (1).

1.1.3 Magnesium

Magnesium is the second most abundant intracellular cation and a vital part of many processes, including intracellular signalling, enzyme activation, bone formation and neuromuscular excitability and serves as a cofactor to protein and DNA synthesis (9,12). The recommended daily intake of magnesium is 12-15 mmol/day, which is usually fulfilled with a well-rounded diet. The daily required amount can be higher during pregnancy or if drug-induced losses are high. Foods that are especially rich in magnesium are green leafy vegetables, nuts, legumes and animal protein (12). The average human body contains about 24g of magnesium, 65% of which is stored in bone mineral and 35% in soft tissue, mostly skeletal muscle (5,12). Only 1% is located in the extracellular space, with serum levels ranging from 0.7-1.1 mmol/l (5,9). About 60% of total serum magnesium is in its free, ionized and biologically active form, whereas 30% are bound to albumin and 10% are complexed to serum anions (9,13). Recommended daily intake is about 300-400mg, with intestinal absorption rates ranging from 25-75%, depending on the diet (5,9). Since extracellular magnesium is mostly ionized, glomerular filtration is high and renal reabsorption is key to maintaining normal magnesium levels and in part regulated by PTH, vitamin D and the calcium sensing receptor (9).

1.1.4 Parathyroid Hormone

The parathyroid hormone (PTH) is one of the key players in calcium and phosphate homeostasis (14,15). The hormone is initially as preproPTH, a 115-amino acid precursor peptide, and later cleaved in the cell, creating PTH (1-84), a straight chain peptide containing 84 amino acids (14,16). This process takes place in the chief cells of the parathyroid glands and is predominantly regulated by extracellular calcium concentrations via the calcium sensing receptor (CaSR), a G-protein coupled receptor reducing PTH synthesis and secretion when calcium is bound. Maximal PTH inhibition occurs at a serum calcium of approximately 2 mmol/l or higher, with only the non-suppressible fraction remaining, whereas maximal PTH secretion generally occurs at 0.5 mmol/l or lower (14). Since intact PTH has a plasma half-life of only a few minutes, 80% of circulating PTH is

inactive fragments awaiting renal filtration (2,5). Normal serum PTH levels range from 15-65 pg/ml and follow a circadian rhythm with significant fluctuations during the day, caused by changes in basal and pulsatile secretion (5,16).

The two major target organs of PTH are the kidney and the bone, showing a high expression of the correlating receptor, termed the PTH/PTHrP receptor type 1 (PTH1R) (14,17). In the bone PTH binds to PTH1R on cells of osteoblastic lineage, enhancing osteoblast activity and proliferation, therefore increasing bone matrix production and mineralization. PTH also induces the production of receptor activator of nuclear factor κ-B ligand (RANKL) and reduces its antagonist osteoprotegerin (OPG), stimulating osteoclastic activity and bone resorption, thus increasing serum calcium and phosphate levels (14,18). Another receptor for PTH is PTH2R, which is expressed in very low levels in most tissues, including the brain, and does not take part in calcium-phosphate metabolism (16).

In the kidney, PTH increases tubular calcium reabsorption and decreases phosphate reabsorption, as well as stimulating the conversion of inactive 25-hydroxyvitamin D to the active metabolite 1,25OHD by promoting transcription of the gene coding for the converting enzyme 1-α-hydroxylase (14,19). In return active vitamin D reduces PTH gene transcription and cell proliferation in the parathyroid glands, lowering PTH secretion closing a negative feedback loop (20). In summary, PTH actions lead to an increase in serum calcium levels, a decrease in serum phosphate levels, an increase in bone turnover and an increase in active vitamin D levels (14).

1.1.5 Vitamin D

Vitamin D encompasses a group of steroid hormones, with ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3) as the two major forms of native vitamin D (16,21). Vitamin D3 is synthesised in the epidermal layer of the skin through UVB irradiation of 7-dehydrocholesterol, forming pre-D3 and later isomerized into D3 (2,21,22). Another source of vitamin D3 are animal-based foods, especially fish oils, whereas vitamin D2 is extracted from plant sources and added to foods, both being mainly absorbed in the small intestine (21). Suggested daily intake is 800 IU vitamin D2 or D3 and can be higher in chronic disease (16,23). Vitamin D2 and D3

have no direct activity and a half-life of 12 to 24 hours. Once diffused into the capillaries, they are bond to vitamin D binding protein (VDB) and mainly absorbed by adipose tissue, muscle and the liver (16). Next 25-hydroxylation by CYP27A1 and CYP2R1 occurs, which are enzymes highly expressed in the liver, and 25-hydroxyvitamin D (25OHD) is formed, also known as calcidiol (16,21). With a plasma life of about 3 weeks, calcidiol is the main storage form of vitamin D and serum levels are indicative of the body vitamin D status, with normal levels above 20-30ng/mL (21,22). Bound to VDB, 25OHD is transported to the kidney and further hydroxylated in the proximal renal tubule cells (16). Involved enzymes are the 1α-hydroxylase CYP27B1 forming 1,25OHD, its physiologically active form termed Calcitriol, and the 24-hydroxylase CYP24A1 forming 24,25-dihydroxyvitamin D, an inactive metabolite (11,21). This process is regulated by Calcitriol itself, PTH and FGF-23 at the gene level, promoting 1α-hydroxylase activity when serum calcium or phosphate levels are low and vice versa (2,16).

Active vitamin D is a key regulator of calcium and phosphate homeostasis and can act directly or through the vitamin D receptor (VDR) on target tissues (16,21,22). Calcitriol enhances renal calcium reabsorption by stimulating the expression of most proteins involved in calcium transport, increases intestinal calcium an phosphate absorption and promotes osteoclast and osteoblast activity in the bone (16). In the parathyroid gland active vitamin D supresses gene expression and cell proliferation reducing PTH secretion (20,21). It is furthermore integral in the responses of immune and nervous systems, shows anticancer and anti-inflammatory actions and promotes cardiovascular health (24). Vitamin D deficiency causes abnormal bone mineralization, presenting as the clinical syndrome of rickets in children and bone pain, low bone mineral density and fractures in adults. Excessive vitamin D levels lead to hypercalcemia and hypercalciuria with symptoms including altered mental status, nausea, constipation, nephrogenic diabetes insipidus, kidney stones and kidney failure (16).

1.1.6 Calcitonin

Calcitonin, produced in the C cells of the thyroid gland, is a potent hypocalcaemic hormone (25,26). Its physiologic role is not yet fully understood, but major actions include the inhibition of osteoclasts, therefore reducing bone resorption, and an increase of renal phosphate excretion, as well as a transient increase in calcium excretion by reducing tubular resorption (27,28). These effects are mainly mediated via the calcitonin receptor and can rapidly reduce serum calcium levels, protecting against hypercalcaemia and maintaining calcium homeostasis (26). Furthermore it is thought to prevent bone loss in times of increased calcium needs, particularly pregnancy, lactation or growth (27). Calcitonin may also, in part, regulate the renal conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D by stimulating the transcription of the 1α-hydroxylase gene (26).

On the other hand, calcitonin is sometimes suggested to be a vestigial hormone, as low or absent calcitonin levels after thyroidectomy as well as increased levels in patients with medullary thyroid carcinoma do not cause any obvious calcium or bone pathologies.

1.1.7 FGF-23

Over the last two decades, fibroblast growth factor 23 (FGF-23) has been identified as an important regulator of phosphate, calcium and vitamin D homeostasis (29,30). FGF-23 interacts with PTH and active vitamin D in a complex, multi-tissue feedback system in order to maintain serum calcium and phosphate levels (30). The main source of FGF-23 are osteoblastic cells, that secrete the growth factor in response to increased calcium and phosphate or elevated PTH and calcitriol (29). FGF-23 increases renal phosphate secretion and decreases reabsorption. Additionally, it reduces α1-hydroxylase activity and lowers 1,25-dihydroxyvitamin D levels (29,30). In the parathyroid gland FGF-23 can lower both PTH secretion and gene expression, therefore lowering calcium, phosphate and calcitriol levels (29). Recent studies also suggest a potential role of FGF-23 in functional iron deficiency and supressing erythropoiesis (31–33), although further research is necessary to fully understand the complex roles of the fibroblast growth factor 23 (29).

1.2 Definition

Hypoparathyroidism (HPT) is a rare endocrine disorder characterised by inadequate parathyroid hormone (PTH) secretion or inadequate receptor activation, which leads to low serum calcium, high serum phosphate and elevated fractional excretion of calcium in the urine (34–36).

1.3 Aetiology

1.3.1 Postsurgical hypoparathyroidism

By far the most common cause of transient (<6 months) or chronic (>6 months) HPT is removal or injury to the parathyroid glands during neck surgery, being responsible for approximately 75% of all HPT cases (36,37).

This occurs due to devascularisation of the glands intra-operatively, their accidental or intentional removal and autotransplantation awaiting revascularisation and recovery of function (38). As a result, intra- and post-operative PTH secretion can be reduced and is a predictor for transient hypocalcaemia and HPT (39,40). Other predictors include levels of preoperative calcium, low preoperative 25-hydroxyvitamin D and low postoperative magnesium levels. Risk factors include autoimmune thyroid disease, such as Graves' disease, central neck dissection, a low-volume thyroid surgeon, prior central neck surgery and other factors. Inability to identify the parathyroid glands during surgery also increases the risk for postsurgical HPT (35,39,41). In some cases post-operative HPT can present years after neck surgery (42).

After total thyroidectomy transient HPT is a very common complication with a median incidence ranging from 19% to 38%. Chronic HPT (>6 months) following neck surgery is less common ranging from 1% to 3% in experienced centres (41,43). The risk of incidental parathyroidectomy in thyroid surgery can be as high as 31% and is reduced by careful dissection performed by a highly experienced surgeon (44). Lorente-Poch et al. demonstrated a direct correlation between parathyroid glands remaining *in situ* and the risk of postoperative HPT. With only 1-2 glands remaining, 74% of the patients suffered from hypocalcaemia, 44% from transient HPT and 16% from chronic HPT. With 4 or more glands remaining these

percentages dropped to 35.3%, 13.1% and 2.6%, respectively (45). Removed parathyroid glands can be reimplanted, also known as parathyroid autotransplantation (PA). In this process the parathyroid tissue is fragmented and either directly implanted in intramuscular or subcutaneous pockets or mixed with a saline solution and injected in the intramuscular space. The preferred site for PA during surgery is the sternocleidomastoid muscle. Although there is no clear evidence about the effectiveness of PA, it is estimated to be an important tool to minimize the risk of HPT after thyroid or neck surgery in selected cases (46). Careful dissection, identification and preservation of the parathyroid glands and their vascular supply remains the best way to ensure gland vitality and avoid postoperative HPT (47).

1.3.2 Autoimmune hypoparathyroidism

Autoimmune hypoparathyroidism is the most common nonsurgical cause for HPT (48). In 1966 Blizzard et al. was the first to demonstrate parathyroid antibodies in 38% of the patients with idiopathic HPT, whereas only 6% of the control population were positive (49). Autoimmune HPT can either occur isolated or be part of the autoimmune polyglandular syndrome 1 (APS-1) (50).

APS-1, also known as autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), is a rare autosomal-recessive disorder caused by mutation of the autoimmune regulator gene (AIRE) (51,52). This leads to circulating autoantibodies and lymphocytic infiltration of the involved organs resulting in organ failure (53).

The major components of the syndrome are hypoparathyroidism, chronic mucocutaneus candidiasis and adrenocortical failure (Addison's disease). If two of these hallmarks are present, the diagnosis of APS-1 is likely and can be confirmed by testing for mutations in the *AIRE* gene.(51,52,54).

Patients usually present with resistant and recurrent mucocutaneus candidiasis in the first 5 years of life. Hypoparathyroidism usually develops before the age of 10 and can be followed by adrenocortical failure during adolescence (52). APS-1 can also appear sporadically in adults, most often in women suffering from Hashimoto thyroiditis (55).

Minor components of the disease are highly variable and can occur years before the first major component emerges and the classic diagnostic criterion is met. These include other endocrine manifestations, like gonadal or testicular insufficiency, gastrointestinal manifestations, like autoimmune gastritis or autoimmune hepatitis and ectodermal manifestations, like chronic keratitis or alopecia (56). These minor components often stem from the AIRE mutation, which puts patients at risk for the development of additional autoimmune diseases over time (51).

In isolated autoimmune HPT or APS-1 autoantibodies can also be directed at the extracellular domain of the calcium sensing receptor (Ca-SR), possibly taking part in the development of hypoparathyroidism (55). In addition Ca-SR activating antibodies have been found, that supress PTH secretion leading to HPT (57).

1.3.3 Genetic causes of hypoparathyroidism

Less than 10% of HPT cases have a genetic cause. Genetic forms of HPT can either be isolated, part of a syndrome or autosomal dominant hypocalcaemia and can occur *de novo* or be congenital (58,59). Although rare, genetic mutations are the predominant cause for HPT in children (60). In many patients with idiopathic HPT a genetic cause is suspected, but the underlying genetic defect remains unknown (34). Due to the high variety of genetic mutations and syndromes associated, only a small part will be portrayed.

1.3.3.1 DiGeorge syndrome

DiGeorge syndrome (DGS), also known as 22q11.2 deletion syndrome, has a heterogeneous presentation including hypoparathyroidism, outflow tract defects of the heart, immunodeficiency due to thymic aplasia, cleft palate, dysmorphic facies and renal abnormalities with impaired kidney function as well as variable cognitive delays and psychiatric illnesses (61,62). Up to 60% of children with HPT have been diagnosed with DiGeorge syndrome (60). 70% - 80% of DGS patients carry a hemizygous microdeletion within 22q11.2 chromosome region, which is referred to as DGS type 1 (61,63). The deleted region harbours TBX1, which encodes a T-box transcription factor. Mutations in TBX1 explain the major phenotypical

features of DGS type 1 (64). DGS type 2 is caused by chromosome 10p deletions and can be indistinguishable from DGS type 1 in its clinical presentation (34,65). Because of the phenotypic variability, the 22q11.2 deletion syndrome has been summarized in the mnemonic CATCH-22, for cardiac defects, abnormal facies, thymic hypoplasia, cleft palate and hypocalcaemia with deletion of chromosome 22q11 (62).

1.3.3.2 Autosomal dominant hypocalcaemia (ADH)

ADH encompasses two distinct genetic disorders, differentiated in type 1 and type 2, being caused by gain-of-function mutations of the calcium sensing receptor (CaSR) and $G_{11}\alpha$ proteins, respectively. About 70% of all ADH patients suffer from type 1 (66–68). PTH concentrations of these individuals are often within the reference range accompanied by a relative hypercalciuria with calcium-to-creatinine ratios above or within the normal range, which is why ADH is considered to be a distinct disease entity from HPT (66). Ectopic calcifications of the kidneys and basal ganglia can be found in more than 35% of ADH patients (67). Treatment with active vitamin D metabolites often leads to severe hypercalciuria and nephrocalcinosis and in severe cases even to renal failure (34). Patients with ADH type 2 present with similar symptoms, but renal complications occur less often (69,70).

1.3.4 Other causes

Both magnesium excess and deficiency can lead to HPT. The magnesium homeostasis is, in part, regulated by CaSR-dependent renal reabsorption (71). Extracellular magnesium can stimulate the receptor and inhibit PTH secretion, albeit two- to threefold less potent than calcium (48,71). PTH secretion may also be inhibited if magnesium levels are too low (<0.4mM), known as the “paradoxical block of PTH secretion” (71,72). Underlying mechanisms involve intracellular signalling pathways resulting in CaSR inhibition (71).

In rare cases mineral deposits in the parathyroid gland can lead to HPT. This has been observed in Wilson’s disease and haemochromatosis as well as thalassemia (73,74).

Other rare causes for HPT include metastatic infiltration or radiation-induced destruction of parathyroid tissue (35).

1.3.5 Pseudohypoparathyroidism

First described in 1942 pseudohypoparathyroidism (PHPT) encompasses a heterogenous group of disorders characterized by target organ resistance to PTH (75,76). Typical laboratory findings are hypocalcaemia and hyperphosphatemia in presence of high plasma PTH levels. This indicates inadequate organ response to PTH but can also be caused by chronic renal failure, severe magnesium or vitamin D deficiency, which should be ruled out (34).

1.3.5.1 Pseudohypoparathyroidism 1a

Patients with pseudohypoparathyroidism type 1a can present with mental retardation, short stature, obesity and skeletal deformations, collectively known as Albright's hereditary osteodystrophy (AHO) (36,77). This is caused by a maternally inherited heterozygotic autosomal dominant mutation of GNAS1, encoding $G_s\alpha$, a stimulatory G protein coupled to the PTH receptor (75,77). In type 1a PHPT $G_s\alpha$ activity is reduced to about 50%. In addition to PTH resistance, the majority of patients develop thyrotropin and growth hormone releasing hormone resistance, leading to hypothyroidism and short stature, and less often gonadotropin resistance, leading to hypogonadism (34,58). Paternally inherited GNAS mutations do not result in hormone resistance due to genetic imprinting, although some features of AHO are still present (36). This is classified as pseudo-PHPT and often occurs in families with type 1a PHPT (34).

1.3.5.2 Pseudohypoparathyroidism 1b

In type 1b $G_s\alpha$ activity is only reduced in the proximal renal tubules, resulting in PTH resistance (77). This is caused by microdeletions or defective methylation of regulatory elements of GNAS1 (75). Patients with type 1b show the same biochemical findings as type 1a, but skeletal deformities are usually absent, although some clinical features of AHO can be present (34,37).

1.3.5.3 Pseudohypoparathyroidism 1c

PHPT type 1c is a variant of type 1a and displays the same clinical features of AHO and hormone resistances, however $G_s\alpha$ activity is not reduced (75).

1.3.5.4 Pseudohypoparathyroidism 2

Patients with PHPT type 2 present with PTH-resistant hyperphosphatemia and show a reduced phosphaturic response to PTH administration (34). The underlying cause has yet to be identified (37).

1.4 Epidemiology

The estimated prevalence of hypoparathyroidism ranges from 24 to 34 per 100,000 (58). Women are affected about twice as often as men, with ca. 75% of all cases attributed to postoperative complications (34,58,75). In 2014, because of its rare occurrence HPT was classified as a designated orphan disease by the European Commission, defined as a prevalence below 5 in 10,000 in the European union (78).

1.5 Pathophysiology

The main pathological mechanisms in hypoparathyroidism derive from the lack of PTH secretion or target organ resistance, resulting in hypocalcaemia with or without hypercalciuria, hyperphosphatemia and low active vitamin D levels (34–36). The complex hormonal interactions have been discussed above.

1.6 Clinical Manifestations

Because of the importance of calcium for the human body, hypoparathyroidism affect almost any tissue or organ, including the muscles, brain, kidneys, heart, and bones. Therefore, clinical manifestations can present with a wide range of symptoms. The severity of symptoms is highly individual and ranges from acute to chronic and life-threatening to asymptomatic (79–81). Interestingly, symptoms do not necessarily correlate with biochemical findings.

1.6.1 Hypocalcaemia

Hypocalcaemia is a main laboratory finding of hypoparathyroidism. It is defined as a total serum calcium below 2.2 mmol/l or free ionized calcium below 1.1 mmol/l (5). Signs and symptoms depend on severity of hypocalcaemia and rate of decline and can be influenced by other factors, such as blood-pH level, hypomagnesemia, as well as serum albumin and phosphate levels (35,80). The symptoms of hypocalcaemia will be discussed in the following pages.

1.6.2 Neuromuscular manifestations

Neuromuscular irritability is a classic cardinal symptom of acute hypocalcaemia, usually presenting with muscle and sensory nerve dysfunction (80–82). In hypocalcaemia neurons show a heightened excitability and can fire bursts of high frequency discharges ensuing a single stimulus (83). Sensory nerve dysfunction may present as paraesthesia in the extremities and perioral region (79–81), whereas motor neuron dysfunction manifests as muscle spasms and tetany, ranging from discomforting carpopedal spasms to life-threatening laryngo- and bronchospasms (34,79,84). Typical clinical signs of heightened neuromuscular irritability are Chvostek's and Trousseau's signs (5,35,85). Chvostek's sign is considered positive, if tapping the facial nerve on a specific point (2 cm in front of the ear lobe and 1 cm below the zygomatic process) results in ipsilateral twitching of the upper lip (35,85). Since 25% of healthy individuals demonstrate a positive Chvostek's sign and 29% of patients with hypocalcaemia have a negative sign, it is an unreliable indicator of hypocalcaemia (85). Trousseau's sign is defined as a carpopedal spasm occurring after a few minutes of restricting blood flow to the arm via a sphygmomanometer cuff inflated above systolic blood pressure. It is considered to be both sensitive and specific for hypocalcaemia, with 94% of hypocalcaemic patients being positive and only 1% false positive (85).

Chronic hypocalcaemia leads to elevated muscle enzyme levels and histological changes in skeletal muscles, depending on the duration and degree of hypocalcaemia (86). Patients with HPT also show decreased muscle strength, maximal force and spend more time on the Timed Up & Go test compared to

controls (87). Rare cases of hypocalcaemia induced myopathy secondary to HPT have been reported (88).

1.6.3 Neuropsychological manifestations

Due to hypocalcaemia, patients with hypoparathyroidism are at risk for generalized tonic-clonic or focal motor seizures (80–82,89). Less frequent neurologic symptoms include parkinsonism, extrapyramidal symptoms and cerebellar signs, such as dysarthria and ataxia, with their cause remaining unknown (81,90). Central nervous system calcifications are quite common in patients with HPT and mostly affect the basal ganglia, but can also be found in other regions like the cerebellum and thalamus and are estimated to be the result of an elevated calcium × phosphate product (80–82,91). Prevalence rates of basal ganglia calcification range from 24% to 74% depending on the literature and their influence on illness and symptoms have yet to be fully understood (91–93).

Several studies have demonstrated, that patients with hypoparathyroidism are at an increased risk to suffer from depression and cognitive dysfunction (89,90,94,95). The severity of symptoms is associated with serum calcium levels but often persist despite optimal therapy and can have a substantial impact on the patients quality of life (94,96).

1.6.4 Cardiovascular manifestations

Calcium plays a critical role in the electrophysiological function of myocardial excitation and contraction (97). Hypocalcaemia and rapid decrease of serum calcium levels can cause a prolonged QT interval, T wave abnormalities and a U wave, visible on the electrocardiogram (81,98,99). This facilitates the emergence of arrhythmias, in rare cases torsades de pointes, a life-threatening polymorphic ventricular tachycardia (82). Severe chronic hypocalcaemia can also cause heart failure with reduced left ventricular ejection fraction, reversible with treatment of the hypocalcaemia (97). The underlying pathophysiological mechanism of low serum calcium leading to cardiomyopathy remains unknown (79). Tabacco et al. found an increased risk for cardiovascular autonomic neuropathy in patients with

postsurgical HPT, which is associated with higher fatigability and higher mortality (100).

Several studies have found changes in arterial vascular structure in patients with nonsurgical hypoparathyroidism (93,101,102). Increased intima-media thickness of the aorta, carotid and renal arteries (101) contribute to an increased risk of ischemic heart disease, stroke and other cardiovascular diseases (37,89). A recently published large retrospective cohort study found an increased for various cardiovascular diseases risk in patients with chronic HPT, including atrial fibrillation, tachyarrhythmias, coronary artery disease, heart failure, stroke, cerebrovascular disease and myocardial infarction (103).

1.6.5 Renal manifestations

Although hypoparathyroidism is not directly associated with renal disease, patients often suffer from impaired kidney function, nephrocalcinosis and kidney stones (81,92,104). The latter two are possibly a complication of the conventional treatment with calcium and activated vitamin D, leading to increased renal calcium excretion and hypercalciuria, due to the lack of PTH-mediated reabsorption (81,82). In a cohort study by Mitchell et al. 41% of patients with HPT had an estimated glomerular filtration rate (eGFR) of 60ml/min × 1.73m^2 or lower defined as chronic kidney disease (CKD) stage 3 or higher (5,92). Age, duration of disease, average calcium levels and time spent with relative hypercalcaemia (>2.4 mmol/l) were all negatively correlating with the eGFR, with two patients needing a kidney transplant (92). In another study the risk for kidney stones and renal insufficiency was almost 5 times higher than in the control groups (104). The European Society of Endocrinology therefore recommends monitoring 24-hour urinary calcium excretion every one to two years and renal imaging, if the patient displays symptoms of kidney stones or if serum creatinine levels begin to increase (105).

1.6.6 Skeletal manifestations

Parathyroid hormone is a key regulator of bone remodelling, a process that replaces mature bone with younger, more resilient bone (82). In

hypoparathyroidism PTH is usually low or absent, which leads to low bone turnover and an increase in bone mineral density (BMD) (81,106,107). The quiescent period of the bone is prolonged and the resorption, formation and activation frequency are reduced, resulting in a net gain of bone mass after each remodelling cycle (107,108). Subsequently patients with HPT show an increased trabecular thickness, trabecular number and trabecular connectivity with T- and Z-scores above age- and sex-matched controls, measured by dual-energy X-ray absorptiometry (92,106,109). Despite the severe changes in bone structure the overall fracture risk does not seem to be affected, except the risk of fractures at the proximal humerus and upper extremities, which was higher in patients with nonsurgical HPT and lower in patients with postsurgical HPT (95). Recent studies also found an increased risk for vertebral fractures, which was especially high in post-menopausal women with anticonvulsive therapy (110,111).

1.6.7 Other manifestations

1.6.7.1 Ophthalmological manifestations

The prevalence of cataracts in patients with nonsurgical hypoparathyroidism is about 50%, depending on age and duration of disease (94,112). In a Danish cohort study Underbjerg et al. found the risk of these patients developing cataract 4-fold increased, compared to controls (89).

1.6.7.2 Dermatological manifestations

Dermatological changes in patients with hypoparathyroidism are common and affect skin, hair, and nails. Coarsening of body hair and loss of pubic and axillary hair can be seen in up to 50% of patients, in some cases alopecia areata (113). Most frequent skin changes are xerotic skin, less often pellagra-like skin pigmentation or pustular psoriasis (113–115). Nails of patients can be brittle and ridged, sometimes followed by onycholysis (113).

1.6.7.3 Infection

Multiple studies have shown a significant increase of infections in patients with hypoparathyroidism, especially upper airway infections (89,95,112,116). The risk

of hospitalization due to infection rises with higher plasma phosphate levels and correlates with the number of hypercalcaemic episodes. Higher doses of active vitamin D above 1 µg per day seem to significantly lower the risk of infections, compared to doses below 1 µg per day (112,117).

1.6.8 Quality of life

Many patients suffering from hypoparathyroidism also complain about a reduced quality of life. Using validated measuring tools, like the 36-Short-Form-Health Survey or the WHO-5 Well-being Index, several studies could demonstrate a significant reduction in physical and mental wellbeing of these patients compared to matched controls (87,118–122). This burden is often underestimated by healthcare professionals (118,123). Furthermore, studies have shown that it can take years until the correct diagnosis is made and adequate treatment is initiated, especially in nonsurgical aetiologies (124).

A wide range of symptoms associated with HPT can affect patients physically, mentally, and emotionally. These include fatigue, brain fog, low energy, pain, poor memory, poor concentration, depression, anxiety and many more (118). Changes in serum calcium levels and low calcium play an integral role in many of these symptoms, but it is unclear to what extent. Some patients following standard treatment may still experience symptoms and reduced quality of life, even though calcium and vitamin D levels are stable and within the normal range, indicating that PTH might directly influence well-being (118,120). Long-term adaptation to low serum calcium levels may also impact the severity of symptoms, since nonsurgical HPT-patients show overall better scores in SF-36 than postsurgical patients (118,121).

Compared to conventional therapy, hormone substitution with recombinant human parathyroid hormone (1-84) (rhPTH) seems to improve quality of life more effectively, although studies examining this effect are inconsistent (118).

1.7 Diagnosis

Hypocalcaemia can have many different causes and should always be investigated (35,125). In order to accurately interpret laboratory findings, calcium

should be corrected for albumin levels and pH or, if possible, ionized calcium should be measured (125). Besides an elaborate history, laboratory measurements should include phosphate, magnesium, intact PTH, renal function and vitamin D metabolites (34,35,125). High phosphate can bind calcium and therefore induce hypocalcaemia, as well as hypo- and hypermagnesemia, which inhibit PTH secretion and lower calcium levels (71). Hypocalcaemia can also occur in chronic kidney disease, but is usually accompanied by high PTH, known as secondary hyperparathyroidism (125).

If on two occasions two weeks apart hypocalcaemia and inadequately low PTH levels are found in a patient with normal serum magnesium, the diagnosis of hypoparathyroidism can be made (34,35,125). Normal PTH levels in the presence of hypocalcaemia also indicate an impaired parathyroid function and suggest HPT; this is particularly true for bariatric surgery patients who usually have higher baseline PTH levels (53). In patients with HPT of unknown origin genetic testing and family screening is recommended to identify the molecular basis of the disorder (53,105).

1.7.1 Laboratory findings

This is a brief overview of typical laboratory findings in patients with untreated hypoparathyroidism (37):

Hallmarks:

- Hypocalcaemia
- Inadequately low or undetectable PTH

Additional findings:

- Low normal to low levels of 1,25-dihydroxyvitamin D and often also 25OHD
- Low normal to low bone turnover markers and alkaline phosphatase
- Reduced daily urinary calcium excretion, but increased fraction calcium excretion
- High normal to high phosphate levels

1.8 Therapy

1.8.1 Acute treatment

Patients with HPT can develop acute hypocalcaemia, which is potentially life threatening and requires immediate action. In both acute and chronic hypocalcaemia the treatment goal is normalizing serum calcium levels to low normal levels and minimizing symptoms (82,125,126). In an acute setting, intravenous calcium supplementation is preferred and should be applied through a large venous catheter, since solutions are hyperosmolar (125). To raise calcium levels 1 – 2 g of calcium gluconate, containing 93 mg of elemental calcium per gram, in 50 ml of 5% dextrose in normal saline or water are infused over 15 – 30 minutes (82,125,126). A more rapid intravenous infusion of calcium can cause severe cardiac dysfunction up to cardiac arrest (126). This acute intervention is followed by a prolonged, slower infusion of 6g calcium gluconate in 500 ml of 5% dextrose over 8 – 10 hours with a flow rate of 0.5 – 1.5 mg elemental calcium per kg per hour (125–127). Another option for calcium substitution is calcium chloride 10% solution with 273 mg of elemental calcium per gram (125). It is advantageous if rapid correction is needed, but can cause tissue necrosis in case of extravasation, which is why calcium gluconate is preferred (126).

Throughout the treatment the patients calcium levels should be regularly monitored and hypomagnesemia as well as low vitamin D levels should be corrected (53,82,125). During intravenous calcium infusion cardiac monitoring is advised. Acute hypocalcaemia in patients with HPT should always prompt re-evaluation of the long-term drug regimen to prevent further episodes.

1.8.2 Management of chronic hypoparathyroidism

All patients with chronic HPT should receive treatment if they experience symptoms of hypocalcaemia and/or have and albumin adjusted serum calcium level below 2.0 mmol/l (<1.00 mmol/l free calcium). Furthermore, asymptomatic patients with an albumin adjusted serum calcium level above 2.0 mmol/l but below the reference range should be treated to assess if this leads to an improvement of their well-being (105).

The main objectives of treatment in chronic HPT are preventing patients from symptomatic hypocalcaemia and reducing complications (81,82). Several treatment goals have been defined, which can be summarized in 8 points (105,128,129):

1. Treatment should be targeted to maintain calcium levels in the low reference range or slightly below it. If patients in target range are still symptomatic, calcium levels can be raised to the upper part of the reference range, granted that their well-being improves.
2. 24 - hour urinary calcium excretion should stay within the sex-specific reference interval to prevent hypercalciuria, a risk factor renal stone forming.
3. Serum phosphate levels should be within reference range.
4. The serum calcium-phosphate of patients should be lower than 4.4 $mmol^2/l^2$ or 55 mg^2/dl^2. At higher levels there is an increased risk of extra-skeletal calcifications, such as nephrocalcinosis, basal ganglia calcifications and cataract.
5. Because of its direct connection to PTH, magnesium levels should be in the reference range.
6. Patients with HPT should maintain an adequate vitamin D status. Despite treatment with active vitamin D and the impaired hydroxylation of 25OHD to 1,25OHD it is recommended to aim for 25OHD levels above 50 nmol/l (20ng/ml), because of its involvement in a wide range of cellular processes.
7. It is recommended, to implement different, individual therapeutic methods to increase patients' quality of life and achieve treatment goals.
8. Lastly, informing the patient about their disease and educating them increases therapy adherence and compliance and is therefore recommended.

These points are part of the clinical guideline on treatment of chronic hypoparathyroidism in adults by the European Society of Endocrinology from 2015 (105). A new guideline was published in 2022 and suggests the use of PTH

replacement therapy if conventional methods do not suffice, whereas the 2015 guideline advises against routine use because rhPTH (1-84) was only approved by the EMA in 2017 (105,130).

1.8.3 Conventional therapy

Conventional therapy is the backbone of treating chronic HPT. It consists of oral calcium and active/native vitamin D supplementation (82,128). Internationally treatment styles vary in regards to their emphasis on either calcium or active vitamin D and are tailored to the individual patients' needs (128).

1.8.3.1 Calcium supplements

Oral calcium supplementation is almost always needed in patients with HPT. The two main options are calcium carbonate and calcium citrate, with 40% and 21% elemental calcium by weight, respectively (128,129). Calcium carbonate is preferred because it binds phosphate. The absorption is better in low pH environments and should therefore be taken with meals. If low pH conditions are not possible due to proton pump inhibitors or H2 agonists calcium citrate is recommended (131). Recommended doses are around 1 – 2 grams per day. Because of limitations to the intestinal calcium absorption capacity to about 500mg doses should be divided and spread throughout the day. Oral calcium supplements and L-thyroxine substitution should not be taken together because of absorption interference and single ingestions above 500mg are unlikely to benefit the patient because of intestinal uptake limitations (105). About 30% of patients require more than 2 grams per day, in rare cases up to 12 grams (126). In general, higher calcium intake requires a lower dose of active vitamin D in order to reach the first treatment goal and vice versa. However, it is unclear, whether patients benefit from higher calcium doses as it increases the risk of hypercalciuria (105). Nutritional counselling to optimize calcium intake is also useful.

1.8.3.2 Active and native vitamin D

The second elementary part of conventional therapy is vitamin D in addition to calcium supplementation (105,128,129). This is necessary due to the reduced

renal conversion of calcidiol to calcitriol in absence of PTH (82,128). With a half-life of 4 to 6 hours calcitriol is usually administered one to two times per day with an average daily dose of 0.25 to mcg (82,105,128). Alfacalcidiol (1α-Hydroxyvitamin D), which is converted to calcitriol in the liver, can also be used, with doses usually twice as high (82). If serum calcium levels are out of range or the patient is experiencing symptoms of hypocalcaemia the dosage can be gradually changed. These changes should be subtle and only be done every 2 to 3 days in order to avoid sever hypo- or hypercalcaemia (105). Another active vitamin D analogue is dihydrotachysterol, which has a longer time to onset and offset of action compared to calcitriol. Therefore its clinical use has been reduced (126).

Native vitamin D such as cholecalciferol and ergocalciferol, are also recommended in the therapy of HPT to reach 25OHD levels of at least 20ng/ml or 50 nmol/L (105,132). A daily dose of 400 – 800 IU will, in many cases, ensure a 25OHD level above 20 ng/ml (105), but substantially higher doses are usually needed during rhPTH(1-84) therapy.

1.8.3.3 Limitations and side effects of conventional therapy

As mentioned above, many patients need higher doses of active vitamin D and calcium to achieve therapy goals, but even with high dose conventional therapy some patients cannot be controlled adequately. Other patients may simply not tolerate higher doses of calcium or active vitamin D because of gastrointestinal side effects or frequent hypercalcaemic episodes (126).

There is an ongoing discussion about the effects of conventional therapy on long term complications, such as extra skeletal calcifications. Especially high daily doses are thought to increase the risk of nephrocalcinosis and kidney stones (129). However, as of yet it is unclear to what extent calcium and active vitamin D supplementation influence the risk (81,82,126).

1.8.4 Additional Therapies

1.8.4.1 Nutrition

High calcium intake during the day is a key component in the treatment of chronic HPT. As mentioned above daily doses are about 1 – 2 grams but can be

significantly higher. A calcium rich diet is therefore recommended in patients with chronic HPT (128). Dietary calcium sources are considered equal, if not even better than supplementary forms (105,126).However, dairy products can also have a high phosphorous content and therefore negatively affect the disease(128). Low dietary sodium intake is also recommended, as it can lower renal calcium excretion, reduce hypercalciuria, and consequently lower the risk of long term complications such as nephrolithiasis and nephrocalcinosis (53,105,133). Another way to reduce the risk of long term complications is to avoid phosphate rich food sources such as convenience products and cheese spread, which helps lower the calcium phosphate product (105,134). Certain prebiotics, such as galacto-oligosaccharides, have been shown to increase intestinal calcium absorption, but further research is necessary to understand their clinical implications in patients with chronic HPT (135).

1.8.4.2 Thiazide diuretics

Thiazide diuretics can be considered in patients with hypercalciuria, defined as a urinary calcium secretion above 300 mg per day (53,105,129). Hypercalciuria is directly associated with calcium intake and calcium levels. It increases the risk of renal complications in patients with chronic HPT and should be avoided whenever possible (105). However, it is recommended to reduce the patient's dietary calcium and sodium intake as well as reducing daily calcium and, if necessary, increasing active vitamin D dosage to control hypercalciuria. If these changes do not achieve the desired reduction thiazide diuretics should be considered (105). Patients receiving treatment with thiazide diuretics should be regularly monitored. Side effects include renal potassium and magnesium losses as well as blood pressure changes (105,128). Therefore magnesium supplements and/or potassium-sparing diuretics are often prescribed ancillary to thiazide diuretics (128).

1.8.4.3 Magnesium

Hypomagnesemia (<0.75 mmol/l) is often seen in patients with chronic HPT. The cause might be HPT itself but could also be treatment with proton pump inhibitors or diuretics. If patients present with low serum magnesium levels therapy

adjustments, such as the addition of amiloride or supplementation of magnesium, are recommended (105).

1.8.5 Hormone substitution

Although serum calcium levels in many patients can be sufficiently controlled with conventional therapy, it does not resolve the underlying issue of low or absent parathyroid hormone (82). PTH has many functions besides calcium homeostasis, such as bone metabolism and renal calcium reabsorption, that are not addressed in conventional therapy (81). In search of a more physiological treatment option in chronic HPT synthetic (hPTH) and recombinant human parathormone (rhPTH) analogues have been tested and approved for therapy (81,82,126).

1.8.5.1 Indications

Indications for the use of rhPTH (1-84) are not clearly defined and leave some room for interpretation. The United States food and drug administration approved its use in patients with chronic HPT, that cannot be well-controlled (82). However, it is unclear, whether “well-controlled” refers to the serum calcium levels, the extend of complications, the general well-being or all of them. Therefore, leading experts in this field defined more concrete indications for considering the addition of rhPTH (53,129):

- Insufficient control of serum calcium levels with conventional therapy (calcium and active vitamin D)
- Oral calcium intake to control symptoms and/or serum calcium levels exceeds 2.5 g per day or active vitamin D exceeds 3.0 µg per day
- Renal complications including an eGFR below 60 ml/min, reduced creatinine clearance, nephrocalcinosis, stone risk or hypercalciuria
- Calcium-phosphate product above $55 mg^2/dl^2$ ($4.4 mmol^2/l^2$) or hyperphosphatemia
- Reduced quality of life

In case of discontinuation, rhPTH (1-84) should be gradually reduced over several weeks, as abrupt stops can lead to severe hypocalcaemia. Patients

should be monitored tightly during this period and oral calcium and active vitamin D doses adjusted accordingly (53).

1.8.5.2 Parathyroid hormone 1-34

Synthetic human parathyroid hormone (hPTH) was initially developed and used as a treatment for osteoporosis (136). This hPTH, also known as teriparatide, only contains the biologically active part of intact PTH, namely the fragments 1-34 (137). In 1996 Winer et al. demonstrated that treatment of HPT with hPTH (1-34) was possible (137). Because of its short half-life it was soon discovered, that twice or thrice daily subcutaneous injections were superior to once daily regimens (138). Even pump delivery systems can be used, leading to a similar or better calcium homeostasis than regular injections while reducing the overall hPTH (1-34) dosage needed (139).

In comparison to conventional therapy hPTH (1-34) normalized the patient's urine calcium excretion in addition to maintaining serum calcium levels at or slightly below target range (137,138,140). Daily doses usually range from 25 – 100 µg/day divided in two or three doses. They should be adjusted in increments of about 20% increase or decrease until therapy goals are met (141). In a long-term treatment study of children with chronic HPT bone turnover markers were mildly elevated, but no changes to bone mineral density or growth could be found (140). Another study from 2018 also found a reduction of serum phosphate levels and an increased quality of life in patients receiving hPTH (1-34) over a period of 24 months (142). Very recent findings suggest that the dose-response and effects of hPTH (1-34) varies according to the aetiology of HPT, but further research is necessary to fully understand the clinical implications (141).

Possible side effects of hPTH (1-34) in rodents previously included osteosarcoma. This association stems from preclinical trials and has since been disproven in humans (143). Other known adverse reactions are headaches, gastrointestinal effects, hypercalcaemia and hypercalciuria (126). Because hPTH (1-34) was only approved for treatment of osteoporosis in adults over a maximum period of two years, its use as a long-term therapy of chronic HPT in adults and children is still off-label (81).

1.8.5.3 Parathyroid hormone 1-84

Recombinant human parathyroid hormone (rhPTH) (1-84) depicts the full-length in vivo parathyroid hormone (129). It was approved for the treatment of HPT by the United States Food and Drug Administration (FDA) in 2015 and by the European medicines agency in 2017 (144,145). This followed the REPLACE study, a double-blind, placebo-controlled, randomised phase 3 trial conducted in 2013. In this study 48% of the patients receiving rhPTH (1-84) could reduce their calcium and active vitamin D dosage by more than 50% while maintaining normal serum calcium levels, compared to 2% of patients in the placebo group (146).

Besides confirming the efficacy and safety of rhPTH (1-84) over time, long-term studies also found a decreased urinary calcium excretion and an increased bone turnover, while preserving renal function (147,148). Bone turnover markers usually spike during the first year of therapy, after which they return to a higher baseline that is within the normal range, which indicates a more physiologic bone metabolism (82,149).

Tabacco et al. showed an increased quality of life in an open-label trial. Patients receiving rhPTH improved in five out of eight domains of the 36-Item Short Form Health Survey (SF-36). General health, mental health, vitality, social functioning and bodily pain showed improvements over 8 years and patients with lower quality of life experienced a greater improvement (150). On the other hand, the PARADIGHM study found an increased burden of the disease in patients receiving rhPTH (1-84) compared to conventional therapy. They also scored lower on the SF-36 and had symptoms of hypocalcaemia more often (151). As of yet the effect of hormone replacement therapy on quality of life is inconclusive.

Because of its longer half-life rhPTH (1-84) is usually only injected once daily. Typically, treatment starts with a daily subcutaneous injection of 50 µg accompanied by a 50% reduction of the daily active vitamin D dose. After several weeks the rhPTH (1-84) dose can be increased or decreased in increments of 25 µg up to a maximal dose of 100 µg per day to reach therapy goals. In the best case, active vitamin D can be discontinued and daily calcium dosage can be reduced to 500 mg or even stopped (53,129).

2. Material and Methods

In this retrospective observational study, we analysed patients with hypoparathyroidism registered in the medical information system (MEDOCS) of the Styrian hospital association (Steiermärkische Krankenhausanstaltengesellschaft/ KAGes). We collected data from 2005 to 2022. No restrictions were made regarding sex and age of the patients.

The primary goal of this study was the continued evaluation of patients with chronic HPT and, in part, continuing the work by Martin Kern published as a thesis in 2015 (152). Special emphasis was placed on the recently approved therapy with recombinant human parathormone (1-84). Secondary goals were comorbidities and long-term complications in patients with chronic HPT. Johanna Windisch and Theresa Lerchl, both co-students, were simultaneously working on their thesis. Johanna's is titled "Hypoparathyroidism – renal and skeletal manifestations" and Theresa's "Hypoparathyreoidismus und Fertilität, Schwangerschaft und Stillzeit".

2.1 Data privacy

All patient data was pseudonymised by only using their 5 to 8-digit patient number. Access to data was restricted to Johanna Windisch, Theresa Lerchl and Simon Geiger. Only authorised persons had access to the original data. The results were calculated on servers of the Medical University of Graz.

2.2 Data collection

The inclusion criteria for this study were

- PTH levels below 30 pg/ml
- while being hypo- or normocalcaemic
- with or without therapy
- in 2 measurements at least 6 months apart.

With the help of Gerit Wünsch from the Institute of Medical Informatics, Statistics and Documentation (IMI), we could identify 971 patients that were further split in groups according to text elements in their diagnosis and laboratory parameters:

- Group A included all patients with the wording “hypopara” in their diagnosis-text and was comprised of 204 individuals.
- Group B included all patients with the wording “Thyroidektomie”, “Schilddrüsenoperation”, “Schilddrüsenentfernung” or “Schilddrüsenkarzinom” in their diagnosis-text and was comprised of 162 patients.
- Group C included all patients, that were neither in group A nor in group B and therefore unlikely to have chronic HPT.
- Group D were all patients of group B, that did not overlap with group A. This included 69 patients, that probably had thyroidectomy and showed signs of HPT but did not have the phrase “hypopara” anywhere in their diagnosis-text.

Group D was manually checked for patients with chronic HPT. 8 patients were diagnosed with HPT, but different wording was used. 14 other patients showed signs of HPT like hypocalcaemia and inadequately low PTH and 47 patients showed no signs of HPT. The final group included 226 patients, which were either diagnosed with or had a very high chance of suffering from HPT. This final group was used to gather all following data. After the manual data collection, 35 of the 226 patients were excluded, because they had normal calcium and PTH levels without receiving therapy at the point of evaluation, therefore not fulfilling the inclusion criteria. All laboratory data was provided by IMI in form of excel documents. An overview is given the flowchart below.

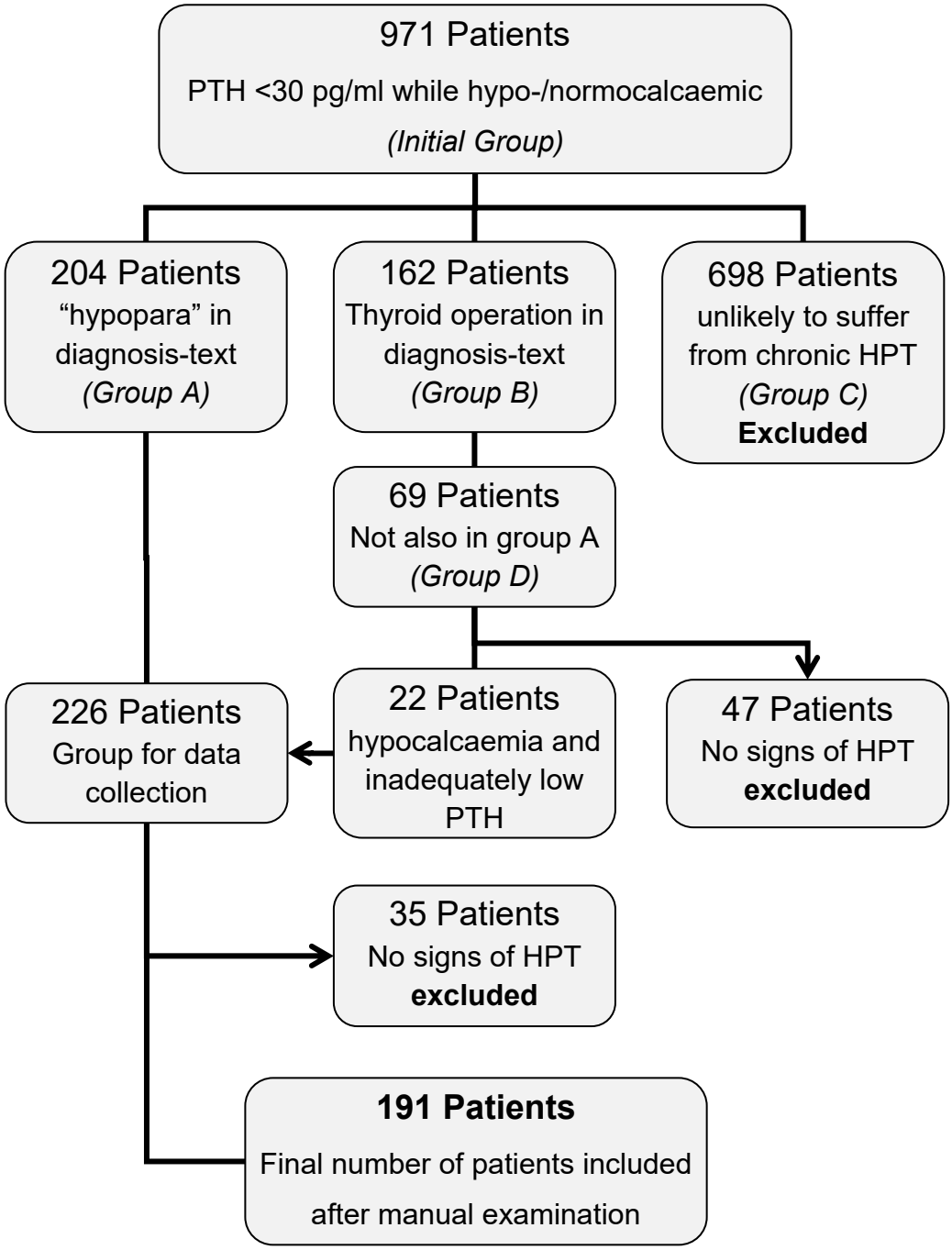


Figure 1: Flowchart of patient selection

2.3 Elements of retrospective data collection

The primary end point was serum calcium at diagnosis. Secondary end points were:

- **Epidemiologic data:** sex, age, weight, height
- **Aetiology of disease:** postsurgical, autoimmune, genetic, others

Figure 2: Flowchart of patient selection

- In postsurgical patients: number of neck operations, type and date of operations, reason for operation and received radioactive iodine therapy
- **Laboratory parameters:** PTH at initial diagnosis and progression, vitamin D and metabolites, total serum calcium, ionised calcium, phosphate, magnesium, creatinine, albumin, calcium-phosphate-product, urine-calcium, haemoglobin, mean corpuscular haemoglobin, mean corpuscular volume, mean corpuscular haemoglobin concentration, thrombocytes, folic acid, vitamin B12, ferritin, transferrin, transferrin saturation, CK, CK-MB, hepcidin, FGF 23
- **Date of diagnosis:** Age at diagnosis and diagnosing hospital
- **Therapy:** frequency and dosage of calcium, vitamin D, thyroid substitution, rhPTH (1-34) and rhPTH (1-84)
- **Other illnesses:** anaemia, hypertension, heart insufficiency, cardiovascular events, diabetes, osteoporosis, tumour-diseases et cetera
- **Symptoms:** tetany, paraesthesia, myalgia, reduced quality of life and others
- **Organ specific long-term complications:** renal insufficiency, dialysis, renal stones, psychiatric diseases, epilepsy, cataract, basal ganglia calcification, other calcifications, bone density changes
- **Hospitalisation** and emergency room visits
- **Fertility:** Pregnancy, complications and nursing periods
- **Infections** including COVID-19

2.4 Statistics

Descriptive statistics included frequencies and percentages as well as mean and median for normal and not-normal distribution, respectively. Distribution was testes using Shapiro-wilk test or graphic demonstration. Mean numbers are followed by the ± - symbol, representing the standard deviation (SD) of the preceding number. Median numbers have their inter-quartile-range (IQR) depicted in brackets that follow. In accordance with distribution the necessary models were used to

demonstrate correlations. Odds ratios (OR) were calculated using linear regression. A p-value of 0.05 was considered significant.
All data was collected using Microsoft Excel® and analysis was done using IBM SPSS Statistics Version 27®.

2.5 Ethics commission

This retrospective observational study with the ethics commission number *33-151 ex 20/21* was approved by the ethics commission of the medical university of Graz on the 5th of February 2021 with a one-year validity, which was extended to the 5th of February 2023.

2.6 Laboratory parameters reference range

Laboratory parameter	Reference range	unit
1,25-dihydroxyvitamin D (1,25OHD)	48 – 110	pmol/l
25-hydroxyvitamin D (25OHD)	30 – 60	ng/ml
Albumin	3.5 – 5.3	g/dl
Total serum calcium	2.20 – 2.65	mmol/l
Ionised calcium	1.15 – 1.35	mmol/l
Creatine kinase myoglobin	0 - 21	u/l
Creatine kinase	0 - 170	u/l
Iron	50 - 160	µg/dl
Estimated glomerular filtration rate (eGFR)	90 – 120	ml/min/1.7m^2
Haemoglobin (Hb)	12/13 -17.5 (male/female)	g/dl
Urea	17.0 – 43.0	mg/dl
Creatinine	0.7 – 1.2	mg/dl
Magnesium (Mg)	0.7 – 1.1	mmol/l
Phosphate (PO)	2.6 – 4.5 0.84 – 1.45	mg/dl mmol/l

Intact parathormone (PTH)	15.0 – 65.0	pg/ml
Ferritin	50 – 400	ng/ml
Transferrin	2.0 – 3.6	g/l
Transferrin saturation (tsat)	16 – 45	%
Fibroblast growth factor 23 (FGF23)	0 – 125	rel-u/ml
Urine-calcium	-	mmol/l
Beta-hcg	0 – 5	mu/ml
Folic acid	2.7 – 34.0	ng/ml
Vitamin B12	180 – 1100	pg/ml
Thrombocytes	140 – 440	10^9/l
Mean corpuscular volume (MCV)	80.0 – 98.0	fl
Mean corpuscular haemoglobin concentration (MCHC)	33.0 – 36.0	g/dl
Mean corpuscular haemoglobin (MCH)	28.0 – 33.0	pg

Table 1: Laboratory parameters with reference ranges and units

2.7 Limitations

Because of the retrospective nature of this study, the amount of information gathered on each patient varies.

All dates, that only consisted of the year, were assumed to be in the middle of the year (01.07.____) and dates, that only had the month and year given, were presumed to be in the middle of the month (15^{th}).

3. Results

3.1 General characteristics of the study population

Overall, our cohort included 191 patients with chronic hypoparathyroidism. 133 (70%) of them were female and 58 (30%) were male. The mean age of the group, excluding deceased patients, was 61.6±19.1 years ± standard deviation (SD), with the youngest and oldest being 10 and 97 years old, respectively. The mean age at diagnosis was 52.1±18.8SD years. Median disease duration was 9 years with an inter-quartile range (IQR) of 10 years.

The most common cause of HPT was postsurgical with 82% (156 patients) followed by idiopathic with 8% (15 patients), genetic with 4% (7 patients) and autoimmune with 3% (5 patients). The aetiology could not be identified in 8 patients (4%).

Hight and weight measurements were available for 68 patients (36%). The average calculated body mass index (BMI) was 27.3±5.8 kg/m^2. The highest was 41.8 kg/m^2 and the lowest 16.3 kg/m^2. 22 of these patients (32%) were overweight with a BMI above 30 kg/m^2.

At the time of evaluation (01.2022) 13 patients (7%) of our cohort had died. Two of those patients died of multiple organ dysfunction syndrome due to sepsis and one died of COVID-19. Other causes of death included myocardial infarction, malignant disease, multimorbidity and complications following kidney transplantation. The cause of death could not be determined in 5 cases. The average age at death was 66.6±11.3 years.

3.2 General characteristics with regards to aetiology

3.2.1 Postsurgical patients

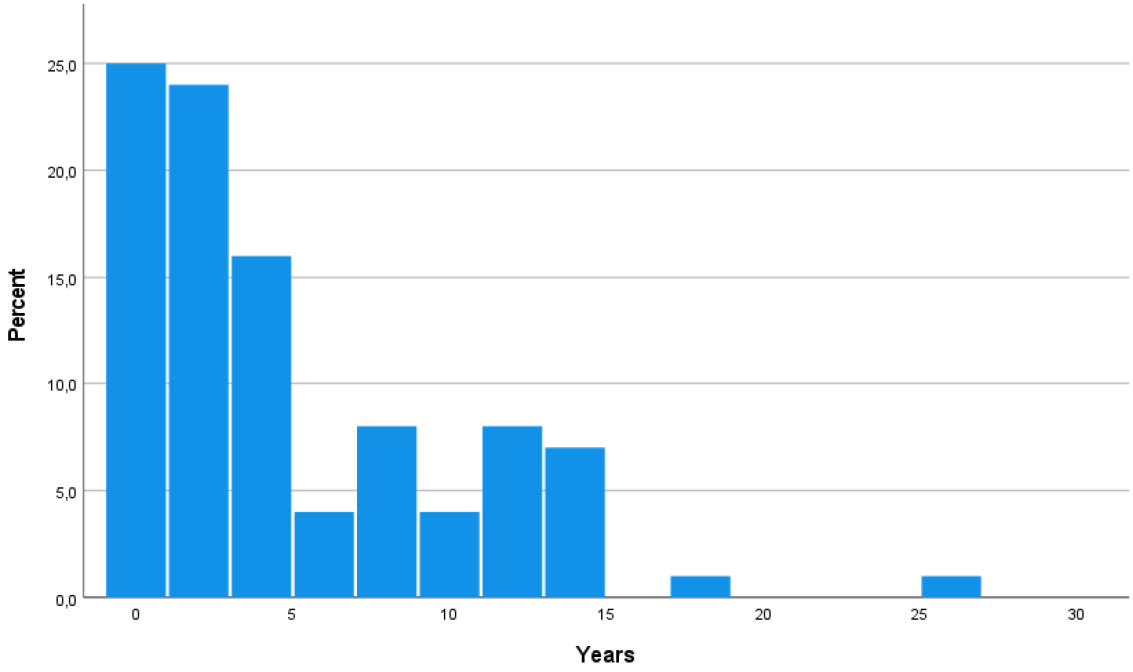
This cohort included 156 patients (82%) that had neck surgery leading to chronic HPT. Gender distribution was similar to overall distribution with 73.7% (115 patients) being female and 26.3% (41 patients) being male. The median time from surgical intervention to diagnosis of HPT was 2.5 (7) years, the longest being 25

years (figure 3). Patients who were diagnosed before 2005 were excluded from this calculation, because their date of diagnosis could not be determined.

122 patients had one neck surgery, 28 had two and 4 patients had three. It was not possible to acquire the number of surgeries from two patients.

The median disease duration was 9 (9) years.

Figure 3: Time from operation to diagnosis

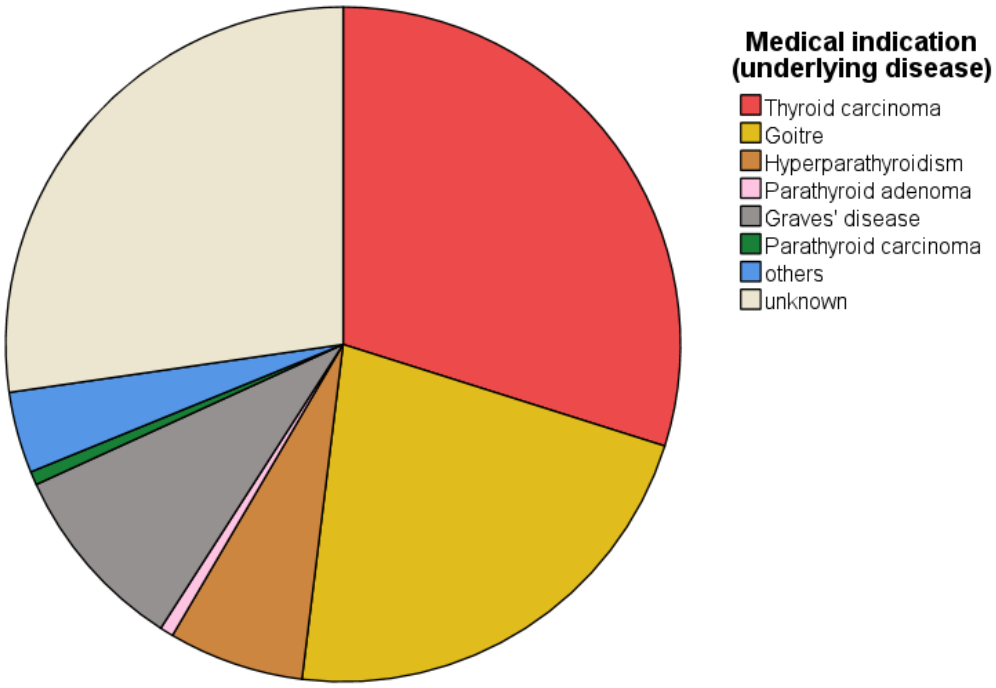


The medical indication for surgical intervention was the following (figure 4):

- 41% (46 patients) had thyroid cancer including papillary and follicular thyroid cancer, but most being not further defined.
- 30% (34 patients) had goitre including unimodular, multinodular and diffuse goitre.
- 13% (14 patients) had Graves' disease
- 9% (10 patients) had hyperparathyroidism
- 5% (6 patients) had other causes, namely chemical burn, cold thyroid nodule, c-cell-hyperplasia, oesophagus carcinoma, suspicious thyroid nodules and MEN2A.
- 1% (1 patient) had parathyroid adenoma
- 1% (1 patient) had parathyroid carcinoma

Unknown causes are excluded from percentages.

Figure 4: Medical indication for surgical intervention



The operations performed were a total thyroidectomy in 118 cases (74.6%), a parathyroidectomy in 8 cases (5.1%), a subtotal thyroidectomy in 7 cases (4.5%), a subtotal parathyroidectomy in 6 (3.8%) and undefined thyroid surgery in 3 cases (1.9%). 4 patients underwent other operations, such as neck dissection or laryngectomy. In addition to the thyroid operation, 9 patients (5.8%) had neck dissection, removing lymph nodes in the area, and in 7 patients (4.5%) autotransplantation of parathyroid tissue was performed. 33 patients received radioactive iodine therapy following surgery.

3.2.2 Other aetiologies

As mentioned above, the underlying causes for HPT of the remaining 35 patients was the following:

- 15 patients (7.9%) had idiopathic HPT, meaning the cause was unknown.
- 7 patients (3.7%) had genetic HPT comprised of 4 patients with DiGeorge syndrome, 2 HDR syndrome (Barakat syndrome) and 1 Kenny-Caffey syndrome.
- 5 patients had autoimmune HPT, 4 of them had APS1.

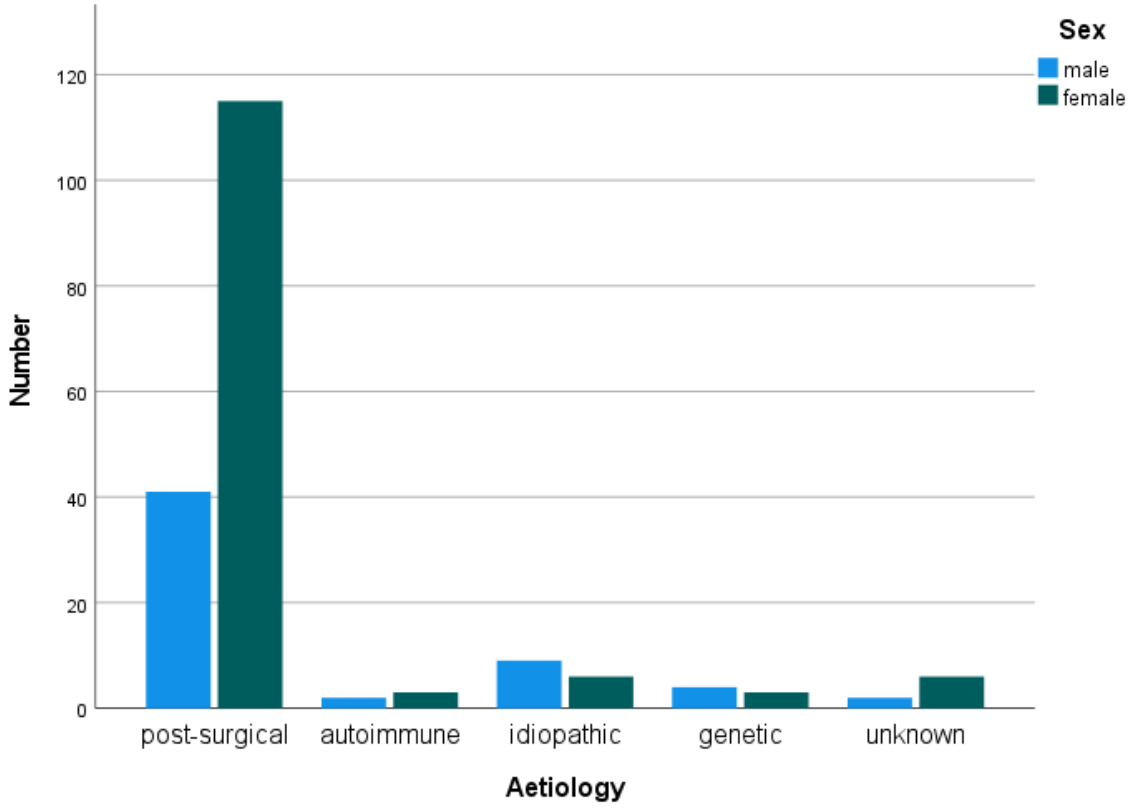
- 8 patients, where the underlying cause could not be ascertained.

Excluding the subgroup with unknown aetiology, nonsurgical patients were on average 9.7 years younger than postsurgical patients (p=0.020; 95%CI [3-16]) and the disease duration was 2.1 years longer (p=0.031; 95%CI [0.2-4.0]).

3.2.3 General statistics regarding sex

More than two thirds of the patients in this study were female. This is due to a high proportion of postsurgical patients being female, coinciding with a higher rate of thyroid disorder in women (153). In our cohort women had an odds ratio (OR) of 3.5 (95% confidence interval (CI) [1.5 – 8.1], p=0.003) to acquire HPT through surgery compared to men. More men suffered from nonsurgical HPT, even though there were fewer male patients in this study (see figure 4). The “unknown” group contained 6 women and 2 men, suggesting that most of these patients were postsurgical. Nevertheless, these patients were excluded from aetiological analysis because they could not provide an aetiology.

Figure 5: Aetiological distribution by sex



The mean age of women and men was 63.7±18.6 and 61.5±19.4 years, respectively. The average disease duration was 9.4±5.2 years for women and 9.6±5.8 years for men. The mean age at diagnosis of the female and male group was 53.8±18.3 and 50.88±19.4, respectively. None of these differences were statistically significant. In the postsurgical group, the average time from surgery to diagnosis for women and men was 3 (8) years and 2 (7) years, also showing no significant difference (p=0.731).

3.3 Laboratory data

3.3.1 Laboratory parameters at diagnosis

Laboratory parameters at diagnosis were acquired by identifying the first blood work at or in the first week following the diagnosis. Because of the long delay between diagnosis and first laboratory data available 134 patients had to be excluded from the following analysis. This was most often either caused by the diagnosis being made before digital data was available, or the diagnosis being made outside of the university hospital. The remaining 57 patients were comprised of 37 women (65%) and 20 men (35%). Aetiologies were divided into 49 postsurgical (86%), 5 idiopathic (8.8%), 1 genetic (1.8%) and 2 unknown (3.5%).

Parameter		Unit	n
Total serum calcium	2.05±0.34	mmol/l	54
Calcium adjusted for albumin	2.02 (0.44)	mmol/l	25
Ionised calcium	0.90±0.15	mmol/l	24
25-hydroxyvitamin D	30.9 (24.4)	ng/ml	44
Phosphate	1.33 (0.4)	mmol/l	43
Magnesium	0.80 (0.10)	mmol/l	28
Albumin	4.30 (0.90)	g/dl	26
PTH intact	14.12±7.63	pg/ml	48
Urine-calcium	2.28 (4.40)	mmol/l	17
eGFR	72.2±28.5	ml/min/1.7^2	35
Haemoglobin	13.25 (1.6)	g/dl	47

Calcium-phosphate product	$mmol^2/l^2$	2.72 (0.8)

Table 2: Select laboratory parameters at diagnosis. Mean is given with SD and median is given with IQR.

Total serum calcium levels were available in 54 patients and had a mean of 2.05±0.34SD mmol/l. The maximum and minimum measured was 3.05 and 1.20 mmol/l, respectively. Hypocalcaemia, defined as a serum calcium level below 2.2 mmol/l was present in 38 patients (70.4%). 13 patients (24.1%) were normocalcaemic. 3 patients (5.6%) were hypercalcaemic (serum calcium > 2.7 mmol/l).

Albumin levels were available in 25 patients, making it possible to adjust serum calcium for albumin according to the following formula:

$$calcium\ adjusted\ for\ albumin = calcium[mmol/l] - (0.025 \times Albumin\ [g/l]) + 1$$

The median serum calcium level adjusted for albumin was 2.02 mmol/l with and inter quartile range (IQR) of 0.44 mmol/l. The adjusted calcium was below 2.2 mmol/l in 19 patients (76%).

24 patients had measurements of their ionised calcium levels. The mean ionised calcium was 0.90±0.15 mmol/l with 22 patients (91.6%) being below the normal range above 1.1 mmol/l.

Serum phosphate levels were available for 43 patients and had a median of 1.33 (0.40) mmol/l, the normal range being 0.84 – 1.45 mmol/l. 13 patients (30.2%) had hyperphosphatemia and 1 patient (2.3%) had hypophosphatemia.

Serum magnesium levels were available for 28 patients with a median of 0.80 (0.10) mmol/l. Hypomagnesemia, defined as a serum magnesium below 0.7 mmol/l was present in 2 cases (7.1%), but no patient had hypermagnesemia.

Intact PTH levels were measured in 48 cases, showing an average of 14.1±7.6 pg/ml, the lowest being 2.4 pg/ml and the highest being 32.9 pg/ml. 28 patients (65.1%) were below the reference range of 15 pg/ml and 15 patients (34.9%) were above it.

Serum albumin levels were available for 26 patients with a median of 4.30 (0.90) g/dl. 6 cases (23.1%) of hypoalbuminemia could be identified.

The median 25-hydroxyvitamin level (44 patients) was 30.9 (24.4) ng/ml, with a maximum and minimum of 76.1 ng/ml and 7.0 ng/ml, respectively. Vitamin D deficiency, defined as 25-hydroxyvitamin D levels below 30 ng/ml, was present in 19 cases (43.2%).

Urine calcium levels were measured in 17 patients with a median of 2.3 (4.4) mmol/l, the highest being 11.2 mmol/l and the lowest being 0.2 mmol/l.

The eGFR at diagnosis was available for 35 patients. The mean eGFR was 72.2±28.5 ml/min/1.7^2, with the lowest and highest being 6.5 and 128.0 ml/min/1.7^2, respectively.

46 Patients had their haemoglobin (Hb) measured, with a median of 13.3 (1.6) g/dl. Minimum and maximum was 6.9 and 16.5 g/dl. Out of 31 women with measurements, 6 (19%) were anaemic, defined as a haemoglobin below 12 g/dl. Out of 15 men, 5 (33.3%) were anaemic (Hb < 13 g d/l). In 10 cases the anaemia type was determinable, showing 3 microcytic/hypochrome and 7 normocytic/normochrome types. None of the microcytic/hypochrome cases had iron deficiency, whereas the normocytic/normochrome had 2 cases of transferrin saturation below 20% and 1 case of ferritin below 30 ng/ml.

The calcium-phosphate product was calculated for 43 patients. The median was 2.7 (0.8) $mmol^2/l^2$. It was elevated (>4.4 $mmol^2/l^2$) in 2 cases.

3.3.1.1 Laboratory data at diagnosis in view of aetiology

There were no significant differences between postsurgical HPT and nonsurgical HPT patients in the parameters mentioned above (table 3).

3.3.1.2 Laboratory data at diagnosis in view of sex

There were no significant differences between women and men in the parameters mentioned above (table 3), even when factoring in aetiology.

3.3.2 Laboratory parameters at last visit

Laboratory parameters were selected by identifying the last entry of each patient. Deceased patients were excluded from analysis in this chapter.

Parameter		Unit	n
Total serum calcium	2.19 (0.3)	mmol/l	140
Calcium adjusted for albumin	2.13 (0.3)	mmol/l	88
Ionised calcium	0.99 (0.1)	mmol/l	10
25-hydroxyvitamin D	35.9 (15.5)	ng/ml	75
Phosphate	1.28±0.23	mmol/l	78
Magnesium	0.80 (0.12)	mmol/l	84
Albumin	4.35 (0.5)	g/dl	88
PTH intact	11.5 (11.9)	pg/ml	79
Urinary calcium (24hr)	2.9 (2.9)	mmol/l	35
eGFR	63.8±26.2	ml/min/1.7^2	127
Haemoglobin	13.3 (2.4)	g/dl	145
Calcium-phosphate product	2.8±0.5	$mmol^2/l^2$	77

Table 3: Select laboratory parameters at last visit

Total serum calcium was available for 140 patients with a median of 2.19 (0.3) mmol/l. The maximum and minimum were 3.23 and 1.36 mmol/l. 72 patients (51%) had a serum calcium below 2.2 mmol/l, 33 (24%) were below 2.0 mmol/l. 10 patients (14%) were hypercalcaemic with a serum calcium above 2.6 mmol/l.

Albumin adjusted calcium could be calculated for 88 patients. The median was 2.13 (0.3) mmol/l, with the highest being 3.2 mmol/l and the lowest being 1.6 mmol. 59 patients (67%) had an albumin adjusted calcium below 2.2 mmol/l and 22 patients (25%) were below 2.0 mmol/l. 3 patients (3%) were above 2.6 mmol/l.

Ionised calcium was measured in 10 patients with a median of 0.99 (0.1) mmol/l. The maximum was 1.1 mmol/l and the minimum was 0.63 mmol/l. 9 out of 10 patients (90%) were hypocalcaemic (< 1.1 mmol/l). No patients were hypercalcaemic.

Serum calcium correlated significantly with albumin (p=0.012) and correlated inversely with phosphate (p=0.026). There was also a positive correlation between calcium and haemoglobin (p=0.028).

25-hydroxyvitamin D was measured in 75 patients. The median was 35.9 (15.5) ng/ml. The highest and lowest were 75 and 15 ng/ml, respectively. 23 patients (31%) were below 30 ng/ml, therefore deficient.

Phosphate was available for 78 patients with a mean of 1.28±0.23 mmol/l. The maximum and minimum were 1.88 and 0.5 mmol/l. 14 patients (18%) had hyperphosphatemia, defined as a serum phosphate above 1.45 mmol/l. Phosphate correlated negatively with albumin (p<0.001) and calcium (p=0.004). There was also a negative correlation between phosphate and haemoglobin (p<0.001), as well as the eGFR (p<0.001).

Magnesium measurements were done in 84 patients. The median was 0.80 (0.12) mmol/l. 9 patients (11%) had hypomagnesemia (<0.75 mmol/l).

Albumin was available for 88 patients with a median of 4.35 (0.5) g/dl. The highest was 5.0 and the lowest was 2.7 g/dl. The albumin was below 3.5 g/dl in 3 cases (3%). Albumin correlated positively with calcium (p=0.012) and negatively with phosphate (p=0.029). There was a significant positive correlation between albumin and haemoglobin (p<0.001), as well as albumin and the eGFR (p<0.001).

Intact PTH was measured in 79 patients. The median was 11.5 (11.9) pg/ml with a maximum and minimum of 163.8 and 1.2 pg/ml.

Urine calcium measurements were available for 35 patients. The median was 2.9 (2.9) mmol/l. The highest was 21.02 and the lowest 0.37 mmol/l. 3 patients (9%) had a urine calcium above 7.5 mmol/l, suggesting hypercalciuria.

The eGFR was measured in 127 patients. The mean eGFR was 63.8±26.2 ml/min/1.7^2. The maximum and minimum were 123 and 4 ml/min/1.7^2.

Haemoglobin was available for 145 patients. The median was 13.3 (2.4) g/dl with the highest being 16.8 g/dl and the lowest 7.5 g/dl. 43 patients (30%) were anaemic at their last visit. Haemoglobin, besides significantly correlating with albumin and calcium, positively correlates with the eGFR ($p<0.001$).

The calcium-phosphate product was calculated for 77 patients. The mean product was 2.8±0.5 $mmol^2/l^2$. The maximum and minimum were 4.6 and 1.2 $mmol^2/l^2$, respectively. 1 patient had a calcium-phosphate product above 4.4 $mmol^2/l^2$, which is considered too high.

3.3.2.1 Laboratory parameters in view of aetiology

The albumin adjusted calcium levels were significantly lower in patients with postsurgical HPT than in nonsurgical patients with a mean difference of 0.18 mmol/l ($p=0.012$; 95%CI [0.04-0.31]).

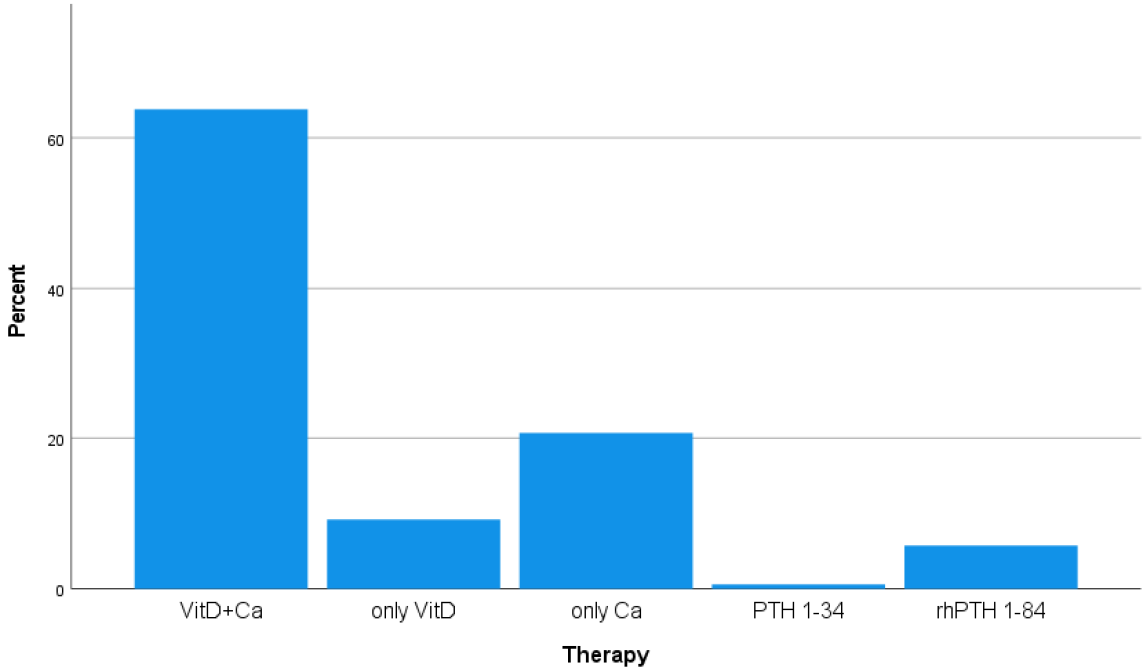
3.3.2.2 Laboratory parameters in view of sex

There were no significant differences in the laboratory parameters at last visit regarding sex.

3.4 Treatment

We had access to treatment data of 188 patients. 169 (90%) were treated with either calcium, activated vitamin D or both. 10 patients (5%) used rhPTH 1-84 and 1 patient (<1%) received teriparatide (figure). 14 patients (7%) did not receive any treatment for HPT.

Figure 6: Medication of patients with HPT



Left to right: Active vitamin D (calcitriol) + calcium (VitD + Ca), only active vitamin D, only calcium, PTH 1-34, rhPTH 1-84

3.4.1 Calcium

111 patients (59%) received calcium in combination with active vitamin D (calcitriol), whereas 36 patients (19%) only received calcium. The median calcium dose was 500 mg per dose with an IQR of 500 mg. The minimum and maximum in a single dose were 100 mg and 2000 mg, respectively. 70 patients (46%) had a single dose above 500 mg and 39 patients (26%) a single dose above 600 mg.

The median frequency was 2 times per day with an IQR of 1. The minimum was every third day, and the maximum was 9 times per day.

The calculated median daily dose for was 1000 (900) mg. The highest daily dose was 5400 mg and the lowest was 200 mg.

The daily calcium supplementation correlated positively with the daily vitamin D dosage ($p<0.001$).

3.4.2 Vitamin D

111 patients received calcitriol in combination with calcium and 16 patients received it without calcium. The medication used as active vitamin D was calcitriol in 124 cases and could not be collected in 3.

The median dose was 0.25 (0.25) µg per application. The minimal single dose was 0.25 µg and the maximal dose per application was 0.75 µg.

The median daily frequency was 1 (1) per day, with a minimum of every third day and a maximum of 5 times per day.

The calculated median daily dose was 0.5 (0.25) µg. The lowest dose per day was 0.08 µg and the highest dose was 2.5 µg per day.

Native vitamin D supplementation was taken by the majority of patients, most commonly in combination with calcium supplementation, for example Cal-D-Vita (600mg calcium + 400 IU vitamin D3). Some patients only took native vitamin D during the winter months and daily intake varied between 400 and 2400 IU. In some cases, vitamin D3 was taken 2-3 times weekly with doses up to 12000 IU.

3.4.3 PTH analogues

1 patient uses hPTH (1-34). She injected 20 µg every second day, resulting in a daily dose of 10 µg. Additionally she took 0.5 µg calcitriol and 1000 mg calcium per day.

10 patients were treated with rhPTH (1-84). They all injected once daily with a median dose of 75 (63) µg. The maximum daily dose was 100 µg and the minimum daily dose was 25 µg. 3 of these patients (30%) did not require active vitamin D therapy.

3.4.4 Thyroxine

146 patients (78%) were substituted with thyroxine. The minimum frequency was every second day, the maximum frequency was twice per day. The median dose was 112 (62) µg, the highest being 250 µg and the lowest being 50 µg.

3.4.5 Therapy in view of aetiology

There were no differences in therapy regarding aetiology.

3.4.6 Therapy in view of sex

The dosage of thyroxine was significantly higher in men, who also weighed more (139µg at 83.1kg versus 111µg at 74.6kg; p <0.001).

3.4.7 Conventional versus hormone replacement

There were significant differences between patients receiving hormone replacement in comparison to those on conventional therapy (calcium, active vitamin D or both).

Average serum calcium and albumin adjusted calcium was higher in patients with hormone replacement therapy, while daily calcium supplementation was lower. 25-hydroxyvitamin D levels were significantly lower in patients with hormone replacement, and 5 out of 7 patients (71%) were vitamin D deficient (<30 ng/ml).
Average eGFR was significantly higher, which was insignificant, when adjusted for age. The mean age of patients receiving hormone replacement was significantly lower. For exact numbers see table 5.

Parameter	Conventional vs. HR	Unit	Average difference	p-value
Total serum calcium	2.2 vs 2.5	mmol/l	0.3 (95%CI [0.1-0.5])	<0.001
Albumin adjusted calcium	2.1 vs 2.4	mmol/l	0.3 (95%CI [0.1-0.5])	0.004
Daily calcium dosage	1092 vs 460	mg	632 (95%CI [7-1190])	0.027
25-hydroxyvitamin D	38 vs 29	ng/ml	9.5 (95%CI [0.2-18.8])	0.045
Age	61 vs 43	Years	20.2 (95%CI [9-31])	<0.001

Table 4: Significant differences in patients receiving hormone replacement (HR) vs. conventional therapy

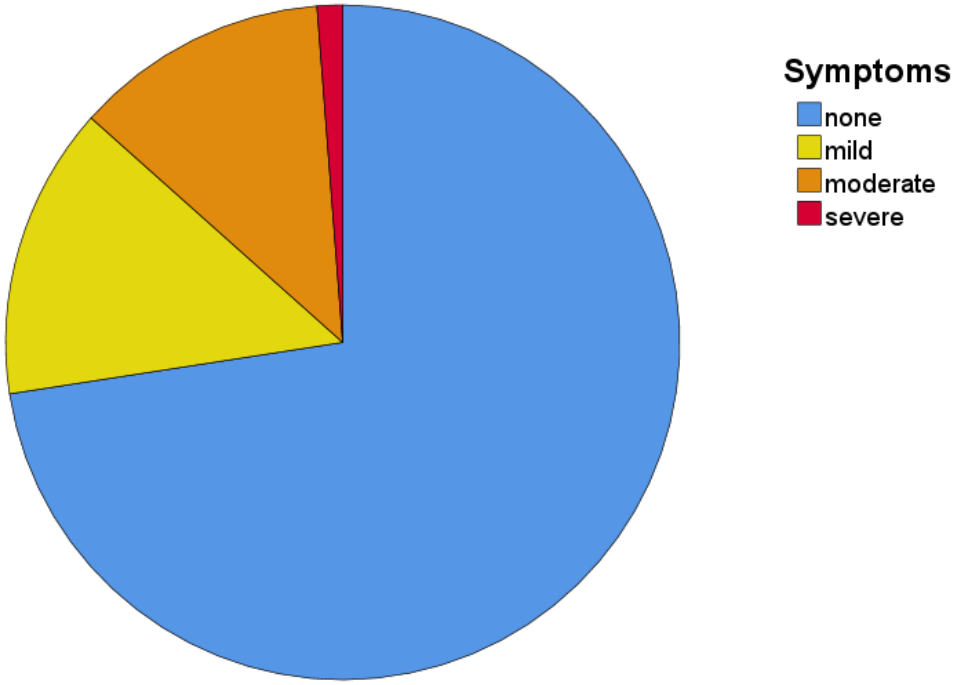
Patients receiving hormone replacement therapy were less likely to develop hypocalcaemia (OR 0.16; p=0.032; 95%CI [0.03-0.86]).

3.5 Symptoms

Out of 164 patients 45 (27%) mentioned symptoms of HPT at their last visit (figure 6). For better evaluation symptoms were grouped in mild, moderate, and severe.

- 23 patients (14%) had mild symptoms, including being relatively free of complaints including mild fatigue, sleeping issues, mild paraesthesia.
- 20 patients (12%) had moderate symptoms, including moderate paraesthesia, dystonia, dyskinesia, ulcerations due to calciphylaxis, psychiatric symptoms and tetanic episodes.
- 2 patients (1%) had severe symptoms including facial and tetanic spasms.

Figure 7: Symptoms in Patients with HPT



20 of these patients (12%) mentioned recent paraesthesia or tetanic episodes. Patients with symptoms had significantly higher daily calcium doses (p=0.018).

3.6 Hospitalization

Since 2005 143 of 188 patients (76%) have been in the hospital. 82 patients (44%) visited the emergency room, and 130 patients (69%) were admitted to the hospital ward. 69 patients (37%) visited both. The reasons for hospital admissions were not collected.

The median number of emergency visits was 0 (1). The minimum was 0 and the maximum was 12.

The median number of hospital ward stays was 1 (3) with a minimum of 0 and a maximum of 28.

The number of emergency room visits correlated positively with the number of secondary diseases (p=0.011). The number of emergency room visits also correlated negatively with the eGFR (p=0.003).

The number of hospital ward stays correlated negatively with the daily calcitriol dose (p=0.026). It also correlated positively with the number of secondary diseases (p=0.004), the number of infections (p=0.025) and the number of emergency room visits (p<0.001).

3.7 Comorbidities

162 out of 181 patients (90%) had one or more comorbidities, most having one (34%), two (28%) or three (13%) additional diseases. The illnesses were grouped according to their prevalence and/or organ system. It was not possible to acquire information about additional diseases in 10 patients, excluding them from this analysis. Unsurprisingly, the number of secondary diseases correlated positively (p=0.008) with the age of patients and the number of emergency room (p<0.001) and hospital ward visits (p<0.001). The following table provides an overview:

Comorbidities	N	Percent	Included diseases
Cardiovascular	61	34%	Arterial hypertension, pulmonary hypertension, myocardial infarction, apoplexy, atrial fibrillation, aortic stenosis, heart insufficiency, cardiomyopathy, coronary heart disease, arteriosclerosis
Renal	49	27%	Polycystic kidney disease, acute kidney injury, thin based membrane disease, membranoproliferative glomerulonephritis, tubulointerstitial nephritis, chronic kidney disease
Malignant disease	31	17%	Following cancers: lung, breast, testicular, cervix, adrenal gland, kidney, liver, prostate, colon, oesophagus, endometroid, melanoma metastases, basalioma, subungual carcinoma, urothelial cancer, Myelodysplastic syndrome, B-cell chronic lymphocytic leukaemia, thrombopenia, chronic myeloid leukaemia, Morbus Waldenström, Hodgkin lymphoma, mantle cell lymphoma

Neurologic	25	14%	Parkinson, migraine, ataxia, polyneuropathy, restless legs syndrome, lumbago, carpal tunnel syndrome, multiple sclerosis, disc prolapse, syncope, Alzheimer, facial nerve paralysis
Diabetes mellitus 2	18	10%	Diabetes mellitus type 2
Metabolic (not DM2)	21	12%	Hyperuricaemia, metabolic syndrome, hyperlipoproteinemia, diabetes mellitus type 1
Obesity	14	8%	Obesity
None	20	11%	
Autoimmune	17	9%	Morbus Addison, haemolytic anaemia, chronic polyarthritis, Crohn's disease, systemic lupus erythematosus, Hashimoto thyroiditis, hepatitis, Sjögren-syndrome, antiphospholipid-syndrome, myasthenia gravis, granulomatosis with polyangiitis, polymyalgia rheumatica
Anaemia	17	9%	Renal anaemia, autoimmune-haemolytic anaemia, iron deficiency anaemia
Osteoporosis	15	8%	Osteoporosis
Endocrinological	14	8%	Acromegaly, hypergonadotropic hypogonadism, hypothyroidism (not iatrogenic), adrenal insufficiency, secondary sterility, polycystic ovary syndrome, primary hyperaldosteronism, high T3 syndrome, diabetes insipidus
Other	13	7%	Sleep apnoea, tracheostoma, iron deficiency, hypervitaminosis D, vitamin D deficiency, ovary cyst, functional asplenia, avascular necrosis, anorexia, Morbus Forestier
Kidney transplant	12	7%	Received kidney transplant
Laryngeal nerve injury	11	6%	Nervus recurrens palsy following surgery
Gastrointestinal	10	6%	Chronic obstipation, liver cirrhosis, pancreatitis, diverticulosis, gastroesophageal reflux disease, choledocholithiasis, cholecystolithiasis
Calcifications	10	6%	Calciphylaxis, calcified tendinopathy, basal ganglia calcification, nephrocalcinosis, cerebellum calcification, renal pelvis calcification
Psychiatric	9	5%	Depression, bipolar, delusion, anxiety disorder
Pulmonary	7	4%	Chronic obstructive pulmonary disease, asthma
Genetic	6	3%	Multiple endocrine neoplasia type 1 and type 2a, Peutz-Jeghers syndrome, autoimmune polyendocrine syndrome type 1, Kenny-Caffey syndrome, DiGeorge syndrome

Benign tumour	5	3%	Uterine fibroid, pituitary adenoma, tongue papilloma
Bone	4	2%	Degenerative spine changes, osteochondrosis
Osteopenia	4	2%	Osteopenia
Epilepsy	3	2%	Epilepsy
Substance abuse	3	2%	Alcohol abuse, pain killer abuse, benzodiazepine abuse
Hereditary dysplasia	3	2%	Fallot-tetralogy, renal agenesis, dysplastic kidneys
Dermatological	2	1%	Calciphylaxis, prurigo, psoriasis
Sarcopenia	2	1%	Sarcopenia
Liver transplant	1	1%	Received liver transplant

Table 5: Table of comorbidities. Percentages were approximated.

Patients with cardiovascular diseases had significantly lower calcium levels. The average difference was 0.14 mmol/l (p=0.006; 95%CI [0.04-0.24]). They also had a lower eGFR on average with a mean difference of 16.7 ml/min/1.7^2 (p<0.001; 95%CI [6.9-26.5]) and visited emergency rooms (p=0.034; 95%CI [0.1-1.4]) and hospital wards more often (p=0.017; 95%CI [0.3-0.6]).

Patients with renal diseases had a higher chance to also have cardiovascular disease (OR 2.8; p=0.004; 95%CI [1.4-5.8]) and were on average more often in hospital wards (3.8 vs 1.9; p=0.007; 95% CI [0.5-3.3]) and emergency rooms (1.7 vs 0.7; p=0.015; 95%CI [0.2-1.8]).

3.7.1 Infections and corona virus disease 2019 (COVID)

56 patients (29%) had documented infections. 11 (20%) of these patients had recurring infections. 4 patients (2%) had COVID. For simplicity different infections were grouped according to their pathogen or organ system involved (table 3). The number of infections correlates significantly (p<0.001) with the number of secondary diseases in patients with HPT.

Infections	N	Percent	Included infections
Respiratory	28	50%	Pneumonia, laryngitis, COVID, bronchitis
Gastrointestinal	12	21%	Heliobacter pylori gastritis, diverticulitis,

			cholecystitis
Urinary tract	9	16%	Urethritis, cystitis, pyelonephritis
Others	9	16%	Phlebitis, infections not further classified, otitis media, tonsillitis, soft tissue infection
Bacterial	7	13%	Borreliosis, Lues, vaginitis, bacteriaemia
Herpes	6	11%	Herpes zoster, genital herpes
Hepatitis C	4	7%	Hepatitis C
Hepatitis B	2	4%	Hepatitis B
CMV	2	4%	Cytomegaly virus
Fungal	2	4%	Fungal stomatitis, candidiasis
Sepsis	2	4%	Staphylococcus aureus, pneumonia

Table 6: List of infections in patients with HPT. Percentages are rounded and relevant to patients with infections.

3.8 Complications

3.8.1 Hypocalcaemia

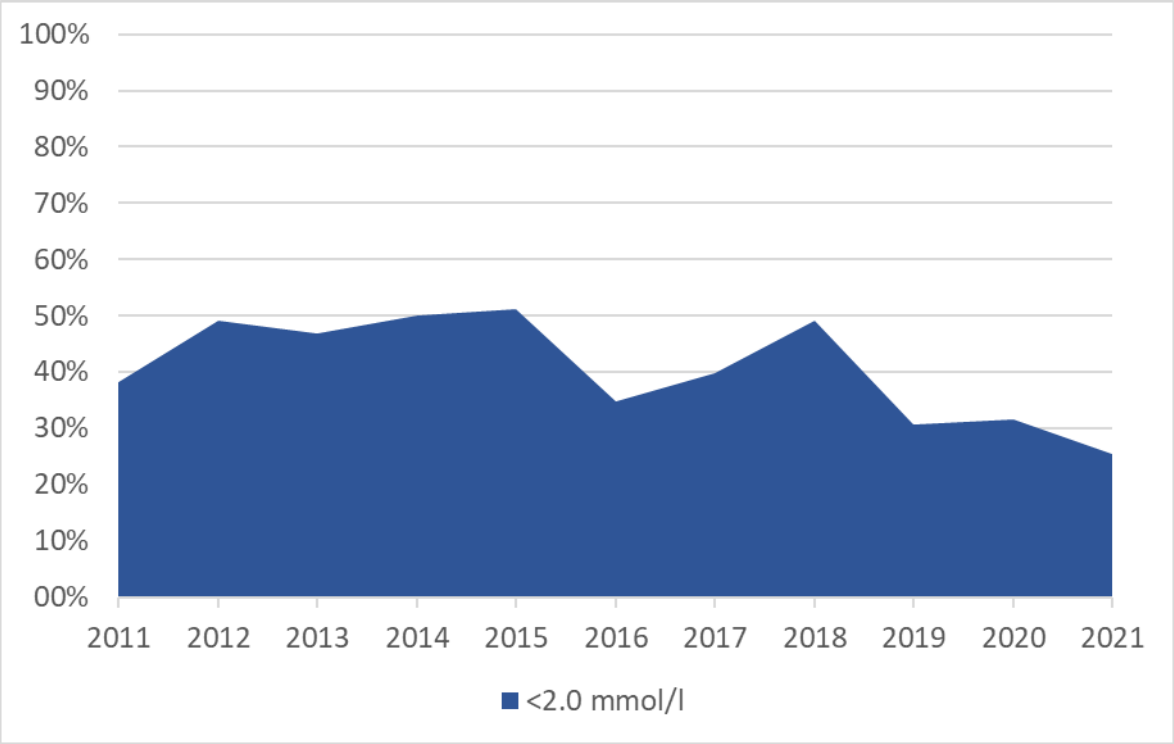
Only using albumin adjusted or free ionised calcium measurements, 65 (70%) out of 94 patients were hypocalcaemic at their last visit (<2.2mmol/l or 1.1mmol/l for ionised calcium). 26 patients (28%) were below 2.0 mmol/l albumin adjusted calcium or 1.0 mmol/l ionised calcium.

With an OR of 3.3 postsurgical patients were more likely to have hypocalcaemia than other aetiologies (p=0.025; 95%CI [1.2-9.3]).

The subgroup of 26 patients with more severe hypocalcaemia (albumin adjusted or ionised calcium levels below 2.0 or 1.0 mmol/l) had on average a disease duration that was 3 years longer than patients above these levels (p=0.026; 95%CI [0.4-5.5]). Patients with cardiovascular secondary diseases were much more likely to develop more severe hypocalcaemia (OR 5; p=0.001; 95%CI [1.9-13.2]), but not patients with renal diseases.

On average, over the last decade (2011-2021), 37% of patients had a median yearly calcium level below 2.0 mmol/l (figure 9). Albumin adjusted calcium or ionised calcium levels were available in 79% of all cases.

Figure 8: Patients with yearly median calcium below 2.0 mmol/l



Percentage of patients with a yearly median calcium below 2.0 mmol/l albumin corrected or <1.0 mmol/l free calcium from 2011 to 2021.

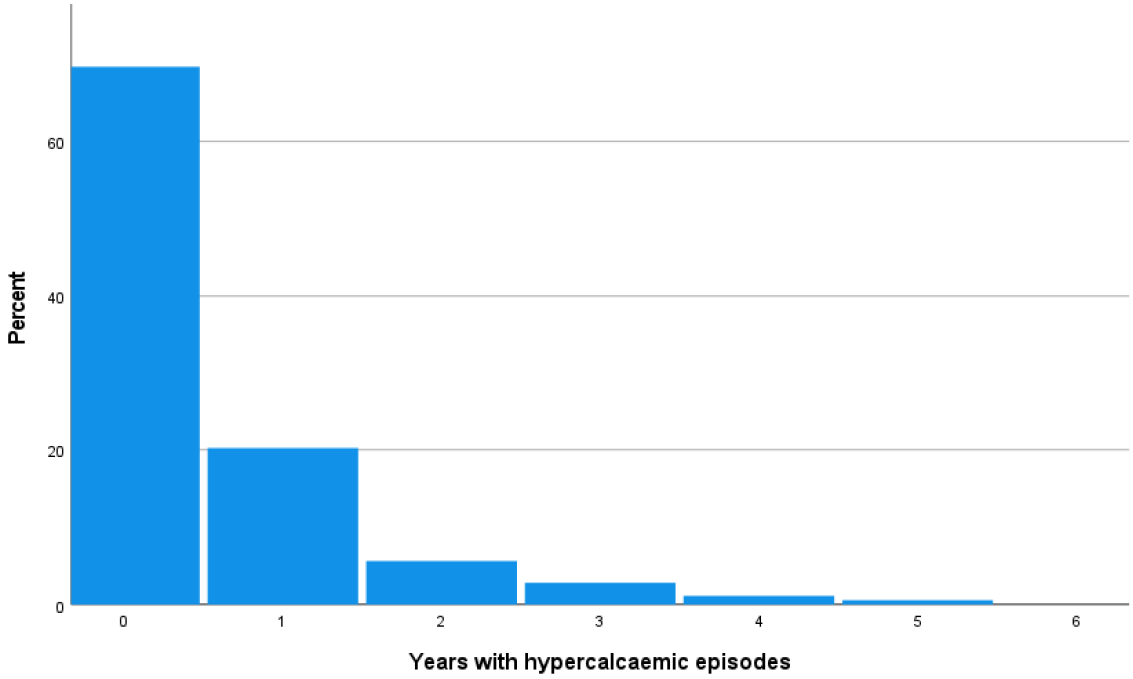
Men were more likely than women to be below 2.0 mmol/l in the yearly median calcium levels (OR 1.48; p=0.011; 95%CI [1.1-2]) and the yearly median haemoglobin was on average 0.42 g/dl lower in patients with more severe hypocalcaemia (p<0.001; 95%CI [0.18-0.67]).

3.8.2 Hypercalcaemia

At the last visit, 10 patients (7%) had a serum calcium or albumin adjusted calcium above 2.6 mmol/l, defined as hypercalcaemia. These patients had on average a disease duration that was 4.2 years longer (p=0.021; 95%CI [0.8-7.6]).

From 2011 to 2021, 48 patients (29%) had at least one year with a hypercalcaemic episode (figure 10).

Figure 9: Years with hypercalcaemic episodes



The number of years with hypercalcaemic episodes correlated positively with the number of infections ($p<0.001$), the number of hospital stays ($p=0.017$) and the number of comorbidities ($p=0.020$).

The number of years with hypercalcaemic episodes was higher in patients with renal diseases ($p<0.001$). Patients with hypercalcaemic episodes had calcifications more often ($p=0.002$).

3.8.3 Psychiatric diseases

Out of 187 patients, 29 (16%) had documented psychiatric diseases. The exact diagnosis was known in 19 cases, 13 (68%) of which were depressions. The other cases included schizophrenia, delusion, delirium, anxiety, and autism.

The number of hospital stays was significantly higher in patients suffering from psychiatric disorders (4 vs 2.4; $p=0.038$; 95%CI [0.1-3.2]).

3.8.4 Epilepsy

8 patients (4%) of our cohort had diagnosed epilepsy. Significantly more men were affected (6 vs. 2; p=0.004; 95%CI [1.2-80]) and patients with epilepsy were younger (49 vs 63 years; p=0.036; 95%CI [1-29]). Nonsurgical HPT patients were more often affected by epilepsy (OR 6.1; p=0.015; 95%CI [1.4-26.9]). Excluding patients with unknown aetiology, 5 (14%) out of 35 nonsurgical patients had epilepsy.

3.8.5 Calcifications

10 (6%) patients had calcifications listed in their medical history, including 7 basal ganglia calcifications, 3 nephrocalcinosis and 2 soft tissue calcifications.

Patients with calcifications had on average a longer disease duration of 4.5 years (p=0.01; 95%CI [1-8]). Men were affected more often (OR 3.7; p=0.048 95%CI [1.01-13.8]) and the risk for calcifications was higher in nonsurgical HPT (OR 5.6; p=0.010; 95%CI [1.5-21.0]).

Patients with calcifications had a significantly higher calcium-phosphate product than patients without (0.24 $mmol^2/l^2$, p<0.001; 95%CI [0.04-0.32].

3.8.6 Renal complications

At the time of evaluation, renal complications were present in 61 (35%) out of 173 patients, excluding deceased patients. 44 patients (25%) were diagnosed with chronic kidney disease grade 3 or worse and 12 patients (7%) have had a kidney transplant. Reasons for kidney transplants were various glomerulonephritis in 6 cases, polycystic kidneys in 2 cases, renal dysplasia, familial nephropathy, reflux nephropathy and nephrocalcinosis following primary hyperparathyroidism.

Comparing the number of patients diagnosed with different CKD stages to the number of patients below certain eGFR thresholds throughout their last year shows the following:

CKD stage	n(d)	median eGFR (ml/min/1.7²)	n(e)	Difference (n)	Difference (%)
Normal or CKD 1/2	127	>60 ml/min/1.7²	84	43	40%

CKD3	30	30 – 59 ml/min/1.7^2	44	14	38%
CKD4	7	15 - 29 ml/min/1.7^2	12	5	53%
CKD5	7	0 - 14 ml/min/1.7^2	5	2	33%

Table 7: Diagnosed [n(d)] and estimated [n(e)] number of patients with CKD using medical documents and the median eGFR over the last year.

Only 145 patients had eGFR measurements with 61 (42%) being below 60 ml/min/1.7^2. The number of patients below an eGFR of 60 ml/min/1.7^2 correlates positively with the number years with at least one hypercalcaemic episode over the last 10 years (1 vs 2; p=0.036; 95%CI [0.4-6.2]).

The median eGFR change in patients with HPT over one year was a reduction of 1.5 ml/min/1.7^2. The highest loss per year was 35 ml/min/1.7^2, while the highest gain per year was 23 ml/min/1.7^2. The median eGFR loss per year correlated positively with the daily calcitriol dose (p<0.001).

3.8.6.1 Dialysis

8 (5%) out of 176 patients needed dialysis at the time of the last visit. Reasons for dialysis were diabetic nephropathy in 4 cases and insufficiency following kidney transplant in the remaining cases. Patients with kidney transplants were more likely to need dialysis (OR 39.7; 95%CI [9.7-162] p<0.001). Patients on dialysis had significantly lower serum calcium (p=0.016) and albumin levels (p=0.003), however, differences in albumin adjusted calcium levels were not significant (p=0.063). The daily amount of calcitriol was significantly lower in patients on dialysis with a mean difference of 0.34 µg per day (p<0.001; 95%CI [0.24-0.45]).

3.8.7 Cataracts

Out of 173 patients, 32 (18%) had documented cataracts. Patients with cataracts were on average 21 years older (p<0.001; 95%CI [16-26]). Adjusted for age, cataracts correlated significantly with the median eGFR reduction (p=0.002) and with the number of years with calcium-phosphate product measurements above

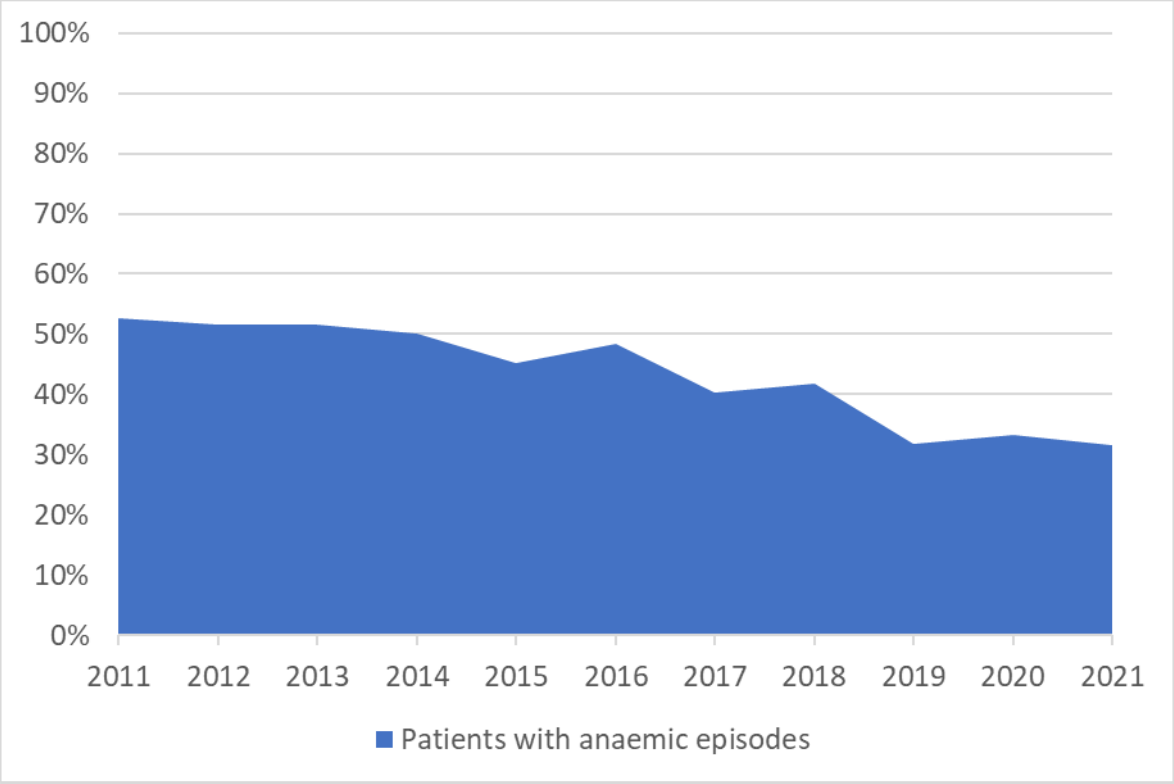
4.4 $mmol^2/l^2$ (p=0.014). There was no significant difference in cataracts between surgical and nonsurgical HPT patients (p=0.504).

3.8.8 Anaemia

At the last visit, 43 patients (30%) were anaemic. Anaemia was defined as a haemoglobin content below 13 g/dl in men and below 12 g/dl in women. Out of 46 men 18 (39%) were anaemic and out of 99 women 25 (25%) were anaemic. 43% of patients with chronic kidney disease grade 3 or worse were anaemic. Where available, MCH and MCV indicated that 92% were normocytic/normochromic and 8% were microcytic/hypochromic.

On average in the last decade (2011-2021) 44% of patients were anaemic at least once each year (figure 7).

Figure 10: Patients with anaemia at least once each year



Patients with anaemia at their last visit were significantly older than patients without, however, when adjusting for sex this correlation became insignificant (p=0.154). Patients with chronic kidney disease stage 3 or worse had a higher risk

of developing anaemia (OR 3.3; p<0.001 95%CI [1.9-10.3]) and the number of comorbidities was higher in anaemic patients (2.6 vs 1.8; p=0.024 95%CI [0.2-1.3]). Anaemic patients had on average an estimated GFR that was 16.9 ml/min/1.7^2 lower than in patients without anaemia (p=0.011; 95%CI [6-28]). The number of hospital ward visits in anaemic patients was 4.1 versus 2.0 in non-anaemic patients (p=0.028; 95%CI [0.2-3.8]).

3.8.8.1 Women with anaemia at last visit

Out of the 25 women with anaemia, 3 (12%) were microcytic/hypochrome and 20 (85%) were normocytic/normochrome. In 2 cases further specifications could not be made. 1 patient had a transferrin saturation below 20% and no patient had a ferritin below 20 ng/ml.

Female patients with anaemia at their last visit had on average a serum calcium, that was 0.21 mmol/ml lower than in women without anaemia (p=0.003; 95%CI [0.1-0.3]). They also showed higher number of comorbidities (1.8 vs 2.8; p=0.029; 95%CI [0.1-2]). Hospital stays occurred more frequently in patients with anaemia (3.3 vs 1.6; p=0.042; 95%CI [0.1-3.2]), with only 6 anaemic women (24%) without any stays, compared to 24 out of 73 (32.4%) in non-anaemic women. The eGFR was on average 14 ml/min/1.7^2 lower than in non-anaemic women (p=0.041; 95%CI [1-27]). There was no significant difference in age (p=0.074) or aetiology (p=0.89).

3.8.8.2 Men with anaemia at last visit

Out of 18 men with anaemia, 14 (78%) were normocytic/normochromic. In 4 cases further specifications could not be made. 3 patients had a transferrin saturation below 20% and 1 patient had a ferritin below 30 ng/ml.

Men with anaemia at their last visit had chronic kidney disease stage 3 or worse more often than those without anaemia (71% vs 11%; p<0.001 95%CI [34-85]). The mean difference in eGFR was 26 ml/min/1.7^2 (p<0.001; 95%CI [6-45]). There was no significant difference in age (p=0.13) or aetiology (p=0.22).

4. Discussion

With 191 patients, this retrospective observational study of patients with chronic HPT is the largest of its kind in Austria. At its heart it is a follow-up to the work done by Martin Kern in 2015, called “Hypoparathyreoidismus – Retrospektive Beobachtungsstudie” (152).

4.1 Study design

This study started 6 years after Kern’s work finished in 2015. Major changes have happened in the field of hypoparathyroidism since then, including the approval of rhPTH(1-84).

The study design of this work differed to some extent from its predecessor. Kern’s study included patients with PTH levels below 25 pg/ml while being normo- or hypocalcaemic treated for chronic HPT between 2004 and 2014 at the Division of Endocrinology and Diabetes, Medical University of Graz. Patients had a minimum age of 18 years and overall Kern could identify 119 patients. Our study included patients with PTH levels below 30 pg/ml while being normo- or hypocalcaemic at two separate measurements at least 6 months apart and did not primarily select patients via diagnosis text. This ensured that the patients selected had chronic HPT (> 6 months). In this follow-up study restrictions to age were not made and we could identify 191 patients in Styria. With an estimated prevalence of 24 – 34 per 100.000, the potential number of patients with chronic HPT in Styria should be in the range of 280 – 400 (58). With 191 patients identified, this process can be considered successful. Compared to Kern’s work, the medical and laboratory data of patients collected was more extensive. This included secondary diseases, infections and other endpoints, such as skeletal and renal outcomes (analysed in a separate thesis by Johanna Windisch) and fertility/pregnancy related endpoints (analyses in a separate thesis by Theresa Lerchl).

4.2 General characteristics

70% of all patients were women, which is slightly less than in Kern’s study (78%). Previous studies, like Mitchell et. al, Gosmanova et al. and Underbjerg et al.

showed similar results with 73%, 76% and 81%, respectively (92,112,154). The mean age of the cohort with 61 years was similar to the previous work, but mean age at diagnosis was lower (52 vs 55), which can be explained by the missing age restriction, and the youngest patient being diagnosed within their first year of life.
82% of all patients had postsurgical HPT, 73% of which were female. The disproportionate amount of women affected is known to be caused by their higher risk of thyroid disorders and therefore higher risk for thyroid operations (153). The median time from operation to diagnosis was 2.5 years, which is shorter than Kern's 5.5 years. A plausible explanation for this difference is the exclusion of patients who were diagnosed before 2005 in this study. Our access was limited to digitalised documents, which generally started in 2004. Many patients with neck surgery between 1960 and 2000 had their first mention of HPT in the hospital information system MEDOCS in 2004. However, there were usually no documents available to determine their exact date of diagnosis, hence these patients were excluded. This may indicate an improvement in the screening program for HPT in patients after neck surgery, especially thyroid surgery.

4.3 Treatment

Conventional therapy was similar across all aetiologies and did not differ between men and women. The median calcium dose was 500 (500) mg taken 2 (1) times per day, resulting in a median daily dose of 1000 (900) mg. At their last visit, 46% of patients had a single calcium dose above 500mg, the highest being 2000mg. According to the guidelines, ingestions above 500mg are unlikely to benefit the patient because of intestinal uptake limitations (105). The high number of patients above 500 mg is, in part, caused by a popular calcium supplement used (Cal-D-Vita®) containing 600 mg calcium and 400 IE cholecalciferol.
Excluding these patients, 26% remained with single doses above 600 mg. This suggests that many patients receive higher single doses than recommended and that the calcium supplementation is not optimized in many cases.

Patients receiving hormone replacement therapy, namely rhPTH (1-84), in addition to conventional therapy had significantly higher calcium levels ($p<0.001$) and a

lower risk of developing hypocalcaemia (OR 0.16; p=0.032). Daily calcium dosage was lower (p=0.027) and 30% of patients managed to discontinue active vitamin D treatment. The increased conversion of 25OHD to 1,25-dihydroxyvitamin D in patients receiving rhPTH (1-84) leads to lower levels of 25OHD and consequently they need a higher vitamin D3 supplementation (155). In line with this, 25-hydroxyvitamin D levels at the last visit were significantly lower (p=0.045) in patients with rhPTH (1-84), and 71% were even vitamin D deficient. Increasing native vitamin D doses to ensure an adequate level of > 30ng/ml is not only inexpensive but also well tolerated and could further stabilize calcium fluctuations and reduce the necessary amount of active vitamin D. However, some patients need relatively high daily doses that some physicians are reluctant to give (ie. 10,000 IU daily and higher).

Patients on rhPTH (1-84) replacement therapy were on average 20 years younger. One explanation for this difference might be that older patients with longer disease duration have learned to live with chronic HPT and stopped looking for new treatment options. The difference could also indicate a bias of physicians towards younger people when prescribing a new and expensive medication.

4.4 Secondary diseases and symptoms

90% of all patients had secondary diseases. Most prevalent were cardiovascular (34%), renal (27%), neurologic (14%) and malignant diseases (13%). It is well known that chronic HPT can cause renal and cardiovascular complications and associations with neurologic diseases have been made (81,103,104).

Patients with cardiovascular diseases had a higher chance of also having renal diseases and vice versa. The number of secondary diseases correlated positively with the number of infections and hospital visits. This indicates that long-term complications of chronic HPT such as renal and cardiovascular diseases are not only a burden for the patient, but also a burden for the medical system. As many experts suggest, efforts should be made to prevent these complications (53,105). However, in many cases the exact cause of these complications is unclear and

therefore their effective prevention still subject of research. Studies with rhPTH (1-84) indicate better renal outcomes compared to conventional therapy, but its broad use in the near future is unlikely due to high costs (148).

27% of patients mentioned symptoms at their last visit and 12% had recent paraesthesia or tetany. In contrast to Kern's study, we did not only include patients with symptoms of hypocalcaemia, but also patients with other symptoms associated with chronic HPT. Not all symptomatic patients had low calcium levels. This might be explained by the fact that typically calcium measurements are performed routinely at certain time points and not when symptoms are most severely present. Moreover, symptoms of hypocalcaemia may not only be caused by low serum calcium levels, but also by rapid changes in these levels, which can even occur while being normocalcaemic (80). They did however receive higher daily calcium doses ($p=0.018$), indicating that doctors tend to increase calcium doses rather than active vitamin D doses if patients complain of symptoms. However, recent studies suggest that not all symptoms in chronic HPT are simply a function of serum calcium levels, but may also be directly associated to the lack of PTH (120).
Symptomatic patients are known to have a lower quality of life and while serum calcium levels can mostly be controlled by conventional therapy, symptoms sometimes cannot (118). Hormone replacement therapy might improve quality of life, but studies on this subject are so far inconclusive. With one fourth of our patients experiencing symptoms despite treatment, the need for further research on improving quality of life is evident.

4.5 Complications

4.5.1 Hypocalcaemia

Hypocalcaemia in patients with chronic HPT is common. Levels between 2.0 and 2.2 mmol/l albumin adjusted calcium are usually tolerated as long as patients are asymptomatic (105). With an odds ratio of 5 ($p=0.001$; 95%CI [1.9-13.2]), patients with cardiovascular diseases were more likely to develop hypocalcaemia below

2.0 mmol/l. Over the past 11 years, 37% of patients had a median yearly calcium below 2.0 mmol/l. In patients with cardiovascular diseases, calcium absorption could be reduced due to the disease itself or because of interaction with other medications. However, it is unclear if these patients are at increased risk for adverse events or an increased mortality because of their low calcium. This could be an interesting subject for further studies.

4.5.1.1 Renal complications and calcifications

Renal complications, especially chronic kidney disease (CKD), are well known long-term issues in patients with chronic HPT (81,154,156). About 25% of our patients were diagnosed with CKD grade 3 or worse. Analysing the median eGFR of our patients in their last year, 42% of patients had an eGFR below 60 ml/min/1.7^2, defined as CKD grade 3. This discrepancy was also found in a large retrospective cohort study by Gosmanova et. al, in which 16% of patients were diagnosed with CKD grade 3 or worse, while 38% of patients had an eGFR below the same threshold (154). The median eGFR lost per year in our cohort was 1.5 ml/min/1.7^2, which is 50% higher than values found in large population studies (157). The yearly eGFR reduction correlated positively with the amount of calcitriol taken per day ($p<0.001$), suggesting the possibility that a higher daily active vitamin D dose negatively affects renal health (158). However, as of yet this correlation is still subject of debate and has not been proven beyond doubt.

Renal and cerebral calcifications were only found in 6% of patients, which is lower than in other studies (93,104). This is likely attributed to the retrospective nature of this study. Patients were not routinely screened for calcifications, and it can be assumed that they were underdiagnosed and underreported.

The 10 patients with calcifications, including 7 basal ganglia calcifications, 3 nephrocalcinosis and 2 soft tissue calcifications, had on average a longer disease duration of 4.5 years ($p=0.01$). Nonsurgical HPT patients were affected more often (OR 5.6; $p=0.010$), and men had a higher risk of developing calcifications (OR 3.7; $p=0.048$). Nonsurgical patients in our cohort also had a longer disease duration ($p=0.031$). Calcifications in our cohort were also linked to a higher calcium-

phosphate product ($p<0.001$) and a higher number of hypercalcaemic episodes ($p=0.002$), which also are known predictors (105).

4.5.1.2 Anaemia

Anaemia was present in 30% of our patients at their last visit and over the past 11 years, on average 44% of patients were anaemic each year. 92% were normocytic and normochromic, which suggest renal disease, chronic disease involvement or both. These assumptions are reinforced by the fact that patients in our cohort with CKD grade 3 or worse had a higher risk of developing anaemia (OR 3.3; $p<0.001$), as well as anaemic patients having higher numbers of secondary diseases ($p=0.024$) and the eGFR being on average 17 ml/min/1.7^2 lower when compared to non-anaemic patients. In a population study on the prevalence of anaemia in patients with CKD about 24% of patients with CKD grade 3 or worse were affected (159). In our cohort, 43% of CKD grade 3 patients had anaemia, which indicates the involvement of additional factors. When adjusted for sex, age did not seem to play a significant role, neither did disease duration or aetiology of HPT. Microcytic, hypochrome anaemias (8%) could mostly be attributed to iron deficiency in women.

Because of the retrospective study design, we cannot fully determine the nature of these anaemias. Hepcidin and erythropoietin or reticulocyte measurements, which could further clarify the origin of these anaemias were not available for our patients (160,161).

Nonetheless, this is a novel and highly relevant finding, as some complaints such as fatigue may be explained rather by anaemia than by hypoparathyroidism itself and should prompt individual assessment and treatment.

4.6 Conclusion

Chronic hypoparathyroidism is a complex disease and long-term complications are highly relevant for many patients. These complications are linked to a lower quality of life. Concomitant diseases such as anaemia and cardiovascular disease are frequent and should prompt specific diagnostic and therapeutic measures. Management and prevention of these complications will be an important field of

future research, as they cause a substantial burden of morbidity and secondary cost, yet many of the mechanisms involved are still largely unknown.

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5. Anhang

5.1 Studienprotokoll

HYPOPARATHYREOIDISMUS

Eine retrospektive Beobachtungsstudie: Update 2021

Charakterisierung von PatientInnen mit Hypoparathyreoidismus am Universitätsklinikum Graz - eine retrospektive Beobachtungsstudie

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1 Wissenschaftlicher Hintergrund

Der Hypoparathyreoidismus ist eine seltene Endokrinopathie, die durch eine zu niedrige Sekretion oder unzureichende Wirkung von Parathormon (PTH) entsteht. Die häufigste Ursache für die Entstehung eines Hypoparathyreoidismus sind die Entfernung oder Verletzung der Nebenschilddrüsen im Rahmen von Operationen im Halsbereich. Als Folge entsteht eine Hypokalziämie, eine Hyperphosphatämie sowie eine erhöhte Kalzium-Ausscheidung im Urin (1–3). Symptome dieser Hypokalziämie sind variabel und reichen von Mattigkeit und Abgeschlagenheit zu Krampfanfällen, Laryngo- und Bronchospasmus bis zu kardialen Arrhythmien und chronischem Nierenversagen (4–7). Häufig beschreiben PatientInnen selbst unter Standardtherapie mit aktivem Vitamin D und Kalzium eine reduzierte „Quality of life“ mit physischen und psychischen Leistungseinschränkungen (1,7). Die konventionelle Therapie mit Kalzium und aktiviertem Vitamin D verbessert zwar die Hypokalziämie, jedoch bleiben andere Folgen des PTH-Mangels unbehandelt, wie verringerte renale Kalziumresorption und erniedrigter Knochenmetabolismus (1,8). Rekombinantes humanes Parathormon (rhPTH(1-84)) wurde 2017 in Europa und 2015 in den USA zugelassen und kann bei entsprechender Indikationsstellung verwendet werden (8). Hauptvorteile dieser neuen Hormonersatztherapie sind eine Verbesserung der Einstellung bei schweren Verlaufsformen trotz Reduktion von aktivem Vitamin D und Kalzium. Effekte auf die Lebensqualität sowie Endpunkt - Langzeitfolgen müssen noch weiter untersucht werden (1,3,8).

Primäres Ziel dieser Diplomarbeit ist die Auswertung retrospektiver Daten der KAGES im Anschluss an die Diplomarbeit „Hypoparathyreoidismus“ von Martin Kern (2015). Sekundär ist die Zusammenlegung der Daten mit einer Diplomarbeit zu diesem Thema aus Wien geplant, um den Aufbau einer großen österreichischen Kohortenstudie zu ermöglichen.

2 Ziel

Ziel dieser Studie ist die aktualisierte Auswertung retrospektiver Daten von PatientInnen mit Hypoparathyreoidismus sowie die Fortführung einer Vorstudie, die als Diplomarbeit 2015 veröffentlicht wurde. Des Weiteren ist nach Abschluss

eine Zusammenführung mit erhobenen Daten aus Wien geplant. Eine vorangehende Literaturrecherche beschäftigt sich mit zugrundeliegenden Pathomechanismen, Ätiologie und aktuellen Therapiemöglichkeiten. Von besonderem Interesse ist hierbei die seit 2017 in Österreich zugelassene Therapie mit rekombinantem Parathormon (rhPTH(1-84)). Laborchemische Daten, u.a. zum Zusammenhang zwischen Nierenfunktion, Mineralhaushalt, Eisenmangel und Hypoparathyreoidismus sowie Endpunktdaten wie Nierensteine, Knochenbrüche, Katarakte, Schwangerschaftskomplikationen, Tumorerkrankungen, etc. werden des Weiteren erhoben.

3 PatientInnen

Das Kollektiv besteht aus PatientInnen, die an KAGES-Häusern bis zum Auswertezeitpunkt 2021 behandelt wurden. Die Identifikation erfolgt über einen Parathormonspiegel von unter 30 pg/ml und gleichzeitig bestehender Hypo- oder Normokalziämie mit oder ohne Therapie.

Beschreibung des PatientInnenkollektivs: Bei Alter und Geschlecht werden keine Einschränkungen vorgenommen. Ein überwiegender Anteil an weiblichen Patienten wird erwartet, da eine häufige Begleiterkrankung die Hypothyreose nach Thyreoidektomie ist.

4 Zielgrößen (Endpunkte)

4.1 Hauptzielgrößen

Die Hauptzielgröße ist das Gesamtkalzium im Serum bei Erstdiagnose, da dieses häufig gemessen wird und gut quantifizierbar ist.

4.2 Nebenzielparameter

- Epidemiologische Daten: Geschlecht, Alter, BMI
- Ätiologie der Erkrankung: postoperativ, autoimmun, genetisch, andere
- Innerhalb der Gruppe mit postoperativem Hypoparathyreoidismus: Anzahl an Operationen im Halsbereich, Art und Datum der Operation,

Feinnadelpunktion und zugrunde liegende Erkrankung bzw. Operationsindikation und erhaltene Radiojodbehandlungen

- Laborparameter: Parathormon bei Erstdiagnose und im Verlauf, Vitamin D und Metabolite, Gesamtkalzium im Serum, ionisiertes Kalzium, Phosphat, Magnesium, Kreatinin, Albumin, Kalzium-Phosphat-Produkt, Harn-Kalzium, Hämoglobin, Ferritin, Transferrin, Transferrinsättigung, CK, CK-MB, Hepcidin, FGF 23
- Datum, betreuende Abteilung und Alter bei Erstdiagnose
- Erkrankungsdauer
- Therapie: Frequenz und Dosis von Kalzium- und Vitamin-D-Präparaten, Schilddrüsenhormon-Substitution, Teriparatid und rhPTH 1-84
- Nebenerkrankungen, u.a. Anämie, Hypertonie, kardiovaskuläre Geschehen, Diabetes, Osteoporose, Tumorerkrankung im Krankheitsverlauf
- Symptome: Tetanien, Parästhesien, Myalgien, eingeschränkte Lebensqualität
- Organspezifische Langzeitkomplikationen: Niereninsuffizienz, Dialysepflicht, Nierensteine, psychiatrische Erkrankungen, epileptische Anfälle, Frakturen, Katarakte, Basalganglienverkalkungen, Knochendichteveränderungen
- Hospitalisationen und Notaufnahme-Besuche
- Fertilität, Schwangerschaft, Schwangerschaftskomplikationen und Stillzeit
- Infektionen, COVID-19
- Soweit verfügbar Daten zur Ernährung

5 Methodik

Über das Institut für Medizinische Informatik, Statistik und Dokumentation sollen im Informationssystem MEDOCS PatientInnen der KAGES mit einem

6 Statistik

6.1 Geplante Auswertung

Die Auswertung erfolgt mittels deskriptiver Statistik.

Für numerische Daten werden Mittelwerte und Standardabweichungen bei normalverteilten und Mediane sowie Interquartilenabstände bei nicht-normalverteilten Parametern berechnet.

Nominale und ordinale Daten werden als absolute und relative Häufigkeiten repräsentiert.

Weiters werden bei ausreichender Fallzahl Korrelationen zwischen Haupt- und Nebenzielparametern dargestellt.

6.2 Fallzahlplanung:

In der Literatur wird eine Prävalenz von ca. 24 / 100.000 beschrieben (9). Somit sollten im Einzugsgebiet der KAGES ca. 280 PatientInnen mit Hypoparathyreoidismus leben. Da aber bei der vorangegangen Datensammlung von 2015 ein PatientInnenkollektiv von 119 Personen erhoben wurde, ist von einer Fallzahl im Bereich von zumindest 150 auszugehen.

7 Datenschutz

Alle Daten werden pseudonymisiert ausgewertet und mit ID-Nummern versehen. Sie sind den PatientInnen nicht zuordenbar. Der Zugang zu den Daten ist ausschließlich Personen, die in das Projekt involviert sind, vorbehalten. Die Auswertung erfolgt an einem Computer des Universitätsklinikum Graz mit Zugangsbeschränkung.

Nur autorisierte Personen haben Zugriff auf die Originaldaten.

8 Nutzen-Risiko Evaluierung

PatientInnen, die in die Studie eingeschlossen werden, haben weder direkten Nutzen von der Studie, noch ist sie für sie mit einem Risiko verbunden, da es sich

um eine retrospektive Analyse handelt. Durch die Pseudonymisierung Vor Analyse sowie vertrauliche Behandlung der Daten und Beschränkung der Zugangsberechtigung ist eine sensible Behandlung der patientInnenbezogenen Daten gewährleistet.

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5.2 Ethikvotum 05.02.2022

Medizinische Universität Graz
Ethikkommission

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Tel.: +43 / 316 / 385-13928, Fax: -14348

VOTUM

gültig bis 05.02.2022

EK-Nummer:	33-151 ex 20/21
Studientitel:	HYPOPARATHYREOIDISM retrospective observational study: update 2021
Prüfer:	PD Dr., MSc Karin Amrein Med Uni Graz
Sponsor:	Medizinische Universität Graz, Klinische Abteilung für Endokrinologie und Diabetologie
Ansprechpartner:	Assoz.-Prof. Priv.-Doz. Dr. Karin Amrein, 8036 Graz, Auenbruggerplatz 15
CRO:	-
Antragsteller:	Medizinische Universität Graz, Klinische Abteilung für Endokrinologie und
Ansprechpartner:	Assoz.-Prof. Priv.-Doz. Dr. Karin Amrein, 8036 Graz, Auenbruggerplatz 15

Die o.a. Studie wurde von der Ethikkommission erstmals im 'expedited Review' am 18.12.2020 behandelt. Die Ethikkommission ist zu folgendem Schluss gekommen:

Es besteht kein Einwand gegen die Durchführung der Studie in der vorliegenden Form.

Kommissionsmitglieder, die für diesen Tagesordnungspunkt als befangen anzusehen waren und daher gemäß Geschäftsordnung an der Entscheidungsfindung und Abstimmung nicht teilgenommen haben: keine

Zur Beurteilung vorliegende Dokumente:

Dokumente eingegangen am 11.12.2020, begutachtet im 'expedited Review' am 18.12.2020	
✓ Antragsformular ECS	11.12.2020
✓ Originalprotokoll DA Studienprotokoll_Ethikkomission Hypopara retrospektiv 2021 1.0	11.12.2020
Dokumente eingegangen am 05.01.2021 (in der nächsten Begutachtung mitbegutachtet)	
✓ Antragsformular ECS unterschrieben	11.12.2020
Dokumente eingegangen am 14.01.2021 (in der nächsten Begutachtung mitbegutachtet)	
✓ Letter of Authorization	14.01.2021
Dokumente eingegangen am 15.01.2021, begutachtet im 'expedited Review' am 05.02.2021	
✓ Cover Letter mit Stellungnahme zur Bearbeitungsmitteilung	02.01.2020

Die Ethikkommission geht - rechtlich unverbindlich - davon aus, dass es sich um keine klinische Prüfung nach AMG bzw. MPG handelt.

Es handelt sich um eine Studie im Rahmen einer Diplomarbeit.

Das Votum der Ethikkommission berührt in keiner Weise die alleinige Verantwortung der Prüferin / des Prüfers / der Prüfer für die ordnungsgemäße Durchführung der Studie unter Einhaltung aller einschlägiger gesetzlicher Bestimmungen und Richtlinien.

Weiters machen wir darauf aufmerksam, dass der Kommission unverzüglich zu melden sind:

- Abweichungen vom Protokoll aus Sicherheitsgründen oder Protokolländerungen

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- Änderungen, die das Risiko der Teilnehmer/-innen erhöhen oder die Durchführung der Studie wesentlich beeinflussen

- Mutmaßliche unerwartete schwerwiegende Nebenwirkungen - SUSARs (AMG-Studien ab 1.5.2004) oder schwerwiegende unerwünschte Ereignisse - SAEs (andere Studien)

- Jegliche Information über sonstige Umstände, die die Sicherheit der Teilnehmer/-innen oder die Durchführung der Studie beeinträchtigen können

zusätzliche Auflagen: Die behördlich vorgeschriebenen Maßnahmen hinsichtlich der COVID-19 Pandemie müssen beachtet werden. Der Prüfer und der Sponsor müssen in ihrem jeweiligen Wirkungskreis unter allfälliger Beachtung von Leitlinien gewährleisten, dass keine zur Bekämpfung der Pandemie benötigten Ressourcen gebunden werden bzw. ausreichend Personal vorhanden ist und die TeilnehmerInnen durch ihre Studienteilnahme keiner zusätzlichen Infektionsgefahr ausgesetzt werden.

Dieses Votum gilt für ein Jahr ab dem Datum der Ausstellung. Bei längerer Studiendauer ist rechtzeitig vor Ablauf der Gültigkeit des Votums ein Zwischenbericht vorzulegen (Berichtsformular), um eine etwaige Verlängerung zu erlangen.

Graz, 05. Februar 2021

Univ.Prof.DI Dr.Josef Haas
Vorsitzender

Univ.Prof.Dr.Hans Dimai
Stv. Vorsitzender

Achtung: Bitte bei allen das Projekt betreffende Schreiben oder telefonischen Anfragen die EK-Nummer angeben!

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5.3 Ethik Verlängerungsvotum

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Ethikkommission

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Tel.: +43 / 316 / 385-13928, Fax: -14348

FOLGEVOTUM
gültig bis 05.02.2023

EK-Nummer:	33-151 ex 20/21 1618-2020
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Zur Beurteilung vorliegende Dokumente:

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Dokumente eingegangen am 15.01.2021, begutachtet im 'expedited Review' am 05.02.2021	
✓ Cover Letter mit Stellungnahme zur Bearbeitungsmitteilung	02.01.2020
Dokumente eingegangen am 02.03.2022, begutachtet im 'expedited Review' am 16.03.2022	
✓ Originalprotokoll 1.1	02.03.2022
✓ Zwischenbericht	02.03.2022
✓ Sonstiges: EK-Meldeformular	02.03.2022

Datum Erstvotum: 05.02.2021

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zusätzliche Auflagen: Die behördlich vorgeschriebenen Maßnahmen hinsichtlich der COVID-19 Pandemie müssen beachtet werden. Der Prüfer und der Sponsor müssen in ihrem jeweiligen Wirkungskreis unter allfälliger Beachtung von Leitlinien gewährleisten, dass keine zur Bekämpfung der Pandemie benötigten Ressourcen gebunden werden bzw. ausreichend Personal vorhanden ist und die TeilnehmerInnen durch ihre Studienteilnahme keiner zusätzlichen Infektionsgefahr ausgesetzt werden.

Graz, 16. März 2022

i.V.

Univ.Prof.DI Dr.Josef Haas
Vorsitzender

Univ.Prof.Dr.Hans Peter Dimai
Stv. Vorsitzender

Achtung: Bitte bei allen das Projekt betreffende Schreiben oder telefonischen Anfragen die EK-Nummer angeben!

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5.4 Poster ÖGKM-Kongress 2020

Eisenmangel bei Hypoparathyreoidismus – Koinzidenz oder häufige unterdiagnostizierte Komorbidität? Ein Fallbericht

Starchl C. [1], Geiger S.[1], Tmava-Berisha A. [2]

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Keywords: Hypoparathyreoidismus, Hypokalzämie, Hyperphosphatämie, Eisenmangel

Hintergrund

Hypoparathyreoidismus ist eine seltene Endokrinopathie, die zu Hypokalzämie und Hyperphosphatämie führt. Dies geschieht entweder durch verminderte Sekretion oder durch inadäquate Antwort auf Parathormon in den Zielgeweben. Mit rund 75 % die häufigste Ursache für einen Hypoparathyreoidismus ist die postoperative Komplikation, wobei meist Frauen nach Schilddrüsenoperation betroffen sind. Komorbiditäten, die mit Hypoparathyreoidismus vergesellschaftet sind, basieren meist auf der Hypokalzämie oder Hyperphosphatämie und umfassen Symptome wie neuromuskuläre Erregbarkeit mit Krämpfen und Parästhesien und in schwereren Fällen Bronchospasmus, Laryngospasmus oder kardialen Arrhythmien. Auch unspezifische Symptome wie Müdigkeit und fehlende Belastbarkeit kommen häufig vor.

Methode

Fallbericht einer prämenopausalen Frau

Resultate

Bei einer 36jährigen Frau wurde nach totaler Thyreoidektomie mit Lymphadenektomie und Megaradiojodtherapie bei papillärem Schilddrüsenkarzinom (pT3b) früh postoperativ ein Hypoparathyreoidismus festgestellt. Unter Standardtherapie mit Vitamin D und Calcium ließ sich keine stabile Situation erreichen, sodass eine Substitutionstherapie mit rhPTH 1-84 1x tgl. sc. eingeleitet wurde.

Trotz Normalisierung des Mineralhaushaltes und Verschwinden der Tetanien und Parästhesien beklagte die Patientin weiterhin eine ausgeprägte physische und psychische Leistungsintoleranz und Fatigue. In den erweiterten Abklärungen zeigte sich eine Eisenmangelanämie (Hämoglobin 11,5 g/dl, Transferrinsättigung 8%, Ferritin 5ng/ml). Nach Korrektur des Eisenmangels durch Eisen-Carboxymaltose 1000mg iv. berichtet die Patientin über weitgehende Beschwerdefreiheit und wiederhergestellte Leistungsfähigkeit.

Conclusio

Dieser Fallbericht zeigt, dass Hypoparathyreoidismus und Eisenmangel nicht zu unterschätzende Komorbiditäten darstellen und sich in ihrer unspezifischen Symptomatik überlappen. Eine korrekte und rasche Diagnose ist für eine bestmögliche Therapie unerlässlich. Komplexe Zusammenhänge könnten sich über erhöhtes FGF-23 bei Hyperphosphatämie ergeben. Bei der Behandlung sollte man an eine durch Calciumpräparate verminderte Eisenabsorption denken und Interaktionen einer Schilddrüsenmedikation mit Eisen beachten. Besonders bei neu aufgetretenem Eisenmangel nach Thyreoidektomie sollte die ursächliche Beteiligung eines Hypoparathyreoidismus in Betracht gezogen werden.

5.5 Poster ÖGKM-Kongress 2021

RETROSPECTIVE OBSERVATIONAL STUDY

Anemia in Hypoparathyroidism - a common companion

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Background. Hypoparathyroidism is a rare endocrine disorder characterized by hypocalcemia and inadequately low parathyroid hormone levels (PTH). Anemia is a common comorbidity in many chronic diseases. We investigated a possible link between hypoparathyroidism and anemia.

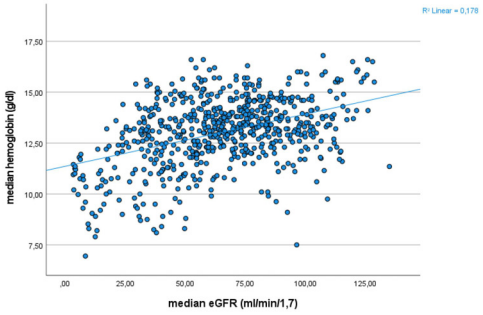
Methods. In a retrospective observational study, we identified 226 patients with hypoparathyroidism in 19 Styrian hospitals and analyzed their laboratory data from 2013 to 2021. We excluded 27 patients because of missing data. Anemia was defined as hemoglobin <12mg/dl for women and <13mg/dl for men.

Results. Overall, 56.3% of all patients were anemic during the observed time period. The investigated cohort had a mean age of 62.4±19.5 years and consisted of 144 women (72.4%) and 55 men (27.6%). 51.4% of all women and 69.1% of all men presented with anemia since 2013. On average, 85 patients had their blood works done per year and we had access to 4±2.5 years of laboratory data per patient. We identified 51 women <55 years ("premenopausal") of which 41.2% had anemia. In anemic premenopausal women 29.3% had a ferritin below 30ng/ml and 44.8% had a transferrin saturation below 20%.

Table 1: Descriptive statistics of the cohort (Hb = hemoglobin)

Cohort	frequency	percent	median Age±SD	median eGFR±SD
Male Hb <13,0	38	69,1	65 ± 18	55 ± 30
Male Hb >13,0	17	30,9	50 ± 20	76 ± 28
total	55	100		
Female Hb <12,0	74	51,4	65 ± 20	53 ± 26
Female Hb >12,0	70	48,6	59 ± 22	70 ± 22
total	144	100		

Figure 1: Scatter plot of hemoglobin and eGFR in patients with hypoparathyroidism



The hemoglobin content of all anemic patients correlated significantly with the estimated glomerular filtration rate (eGFR) (p<0.001). The mean eGFR of patients with and without anemia was 52.8 and 72.7 ml/min/1.7m^2, respectively. The cause of anemia was not determinable in most patients because of missing data, but where available, iron deficiency and renal anemia appeared to be the most common cause.

Conclusions. In patients with hypoparathyroidism, anemia appears to be a very common comorbidity. This is a novel and highly relevant finding, as some complaints such as fatigue may be explained rather by anemia than by hypoparathyroidism and should prompt individual assessment and treatment. Further research is necessary to fully understand the underlying mechanisms.

5.6 Quiz: Schwere Knochen!?

Fallbericht

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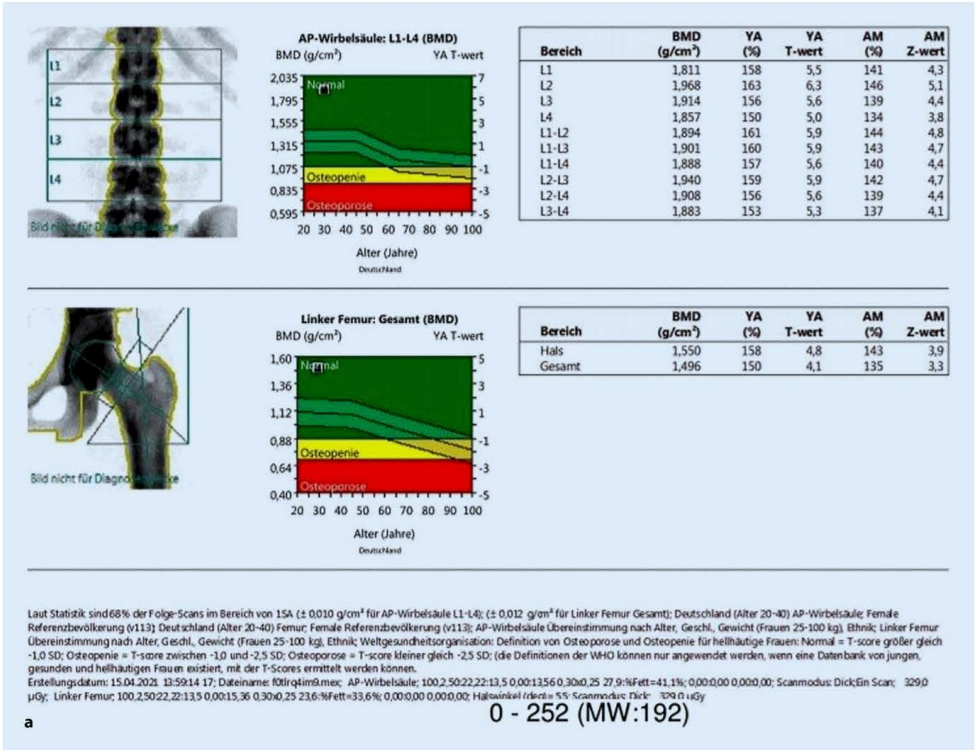
Quiz: Schwere Knochen!?

Fallbericht

Die 29-jährige Frau J. stellt sich im Rahmen einer Kontrolluntersuchung vor. Sie wurde aufgrund eines therapieresistenten Morbus Basedow und eines Knotens in der Schilddrüse im November 2017 thyreoidektomiert, abgesehen von einem BMI von 45 ist sie gesund. In der Knochendichtemessung mittels DXA im April 2021 zeigen sich überdurchschnittlich hohe Werte (◘ Abb. 1).

Welche Ursache könnte die hohe Knochendichte haben?

a) Die Patientin hat an einer klinischen Studie mit Romosozumab teilgenommen.
b) Familiäres Osteopetrose-Syndrom
c) Postoperativer Hypoparathyreoidismus
d) Myelofibrose
e) Morbus Paget

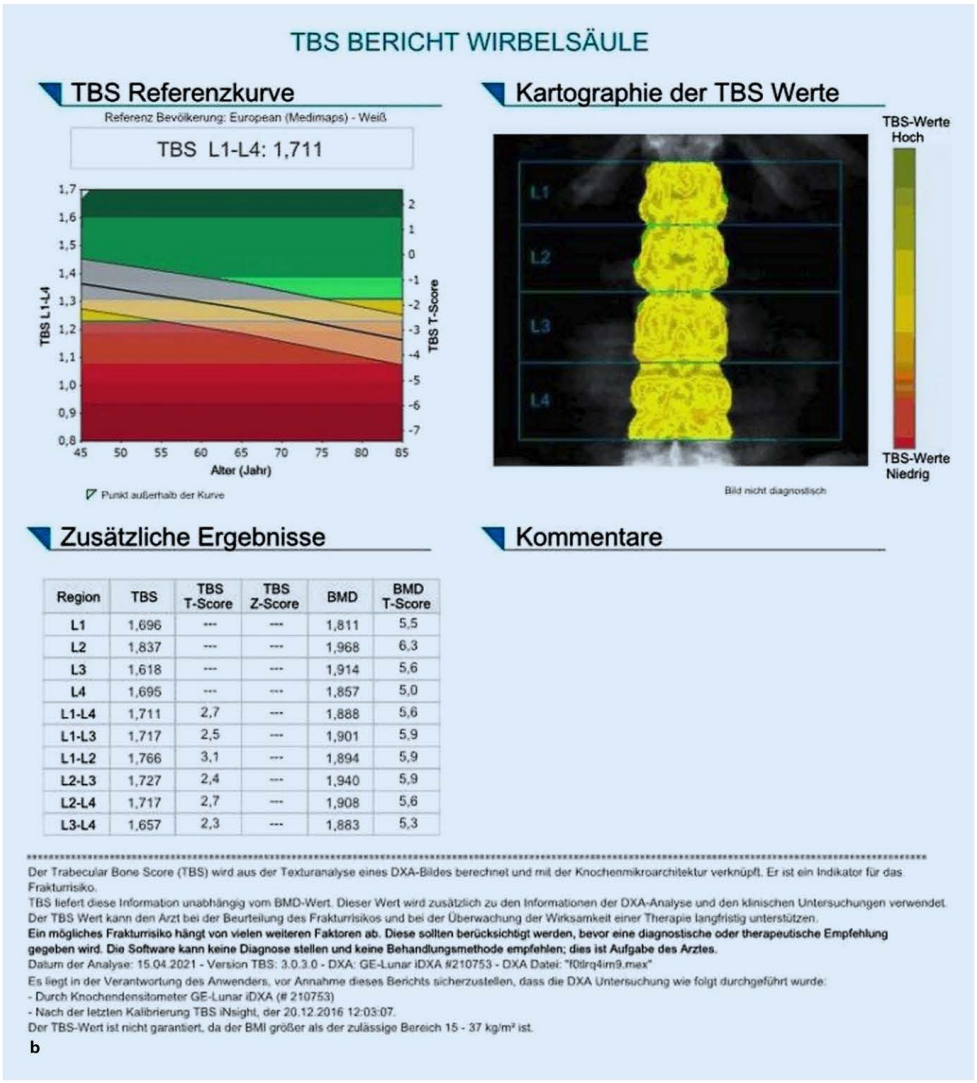


Bereich	BMD (g/cm²)	YA (%)	YA T-wert	AM (%)	AM Z-wert
L1	1,811	158	5,5	141	4,3
L2	1,968	163	6,3	146	5,1
L3	1,914	156	5,6	139	4,4
L4	1,857	150	5,0	134	3,8
L1-L2	1,894	161	5,9	144	4,8
L1-L3	1,901	160	5,9	143	4,7
L1-L4	1,888	157	5,6	140	4,4
L2-L3	1,940	159	5,9	142	4,7
L2-L4	1,908	156	5,6	139	4,4
L3-L4	1,883	153	5,3	137	4,1

Bereich	BMD (g/cm²)	YA (%)	YA T-wert	AM (%)	AM Z-wert
Hals	1,550	158	4,8	143	3,9
Gesamt	1,496	150	4,1	135	3,3

Laut Statistik sind 68% der Folge-Scans im Bereich von 1SA (± 0,010 g/cm² für AP-Wirbelsäule L1-L4); (± 0,012 g/cm² für Linker Femur Gesamt); Deutschland (Alter 20-40) AP-Wirbelsäule; Female Referenzbevölkerung (v113) Deutschland (Alter 20-40) Femur; Female Referenzbevölkerung (v113); AP-Wirbelsäule Übereinstimmung nach Alter, Geschl., Gewicht (Frauen 25-100 kg), Ethnik; Linker Femur Übereinstimmung nach Alter, Geschl., Gewicht (Frauen 25-100 kg), Ethnik; Weltgesundheitsorganisation: Definition von Osteoporose und Osteopenie für hellhäutige Frauen: Normal = T-score größer gleich -1,0 SD; Osteopenie = T-score zwischen -1,0 und -2,5 SD; Osteoporose = T-score kleiner gleich -2,5 SD; (die Definitionen der WHO können nur angewendet werden, wenn eine Datenbank von jungen, gesunden und hellhäutigen Frauen existiert, mit der T-Scores ermittelt werden können.
Erstellungsdatum: 15.04.2021 13:59:14 17; Dateiname: f0tlrq4im0.mex; AP-Wirbelsäule: 100,2,50:22,22:13,5 0,00:13,56 0,30x0,25 27,9:%Fett=41,1%; 0,00:0,00 0,00:0,00; Scanmodus: Dick;Ein Scan; 329,0 µGy; Linker Femur; 100,2,50:22,22:13,5 0,00:15,36 0,30x0,25 23,6:%Fett=33,6%; 0,00:0,00 0,00:0,00; Halswinkel (dext) = 5°; Scanmodus: Dick; 329,0 µGy

Abb. 1 ▲ a DXA-Bericht von Frau J. mit deutlich erhöhten T- und Z-Werten



Region	TBS	TBS T-Score	TBS Z-Score	BMD	BMD T-Score
L1	1,696	---	---	1,811	5,5
L2	1,837	---	---	1,968	6,3
L3	1,618	---	---	1,914	5,6
L4	1,695	---	---	1,857	5,0
L1-L4	1,711	2,7	---	1,888	5,6
L1-L3	1,717	2,5	---	1,901	5,9
L1-L2	1,766	3,1	---	1,894	5,9
L2-L3	1,727	2,4	---	1,940	5,9
L2-L4	1,717	2,7	---	1,908	5,6
L3-L4	1,657	2,3	---	1,883	5,3

Abb. 1 ▲ **b** Trabecular Bone Score (TBS) von Frau J. mit erhöhten T-Werten

Tab. 1 Ausgewählte Differenzialdiagnosen erhöhter Knochendichte
Übergewicht [1]
Primäre Myelofibrose (progrediente Knochenmarkfibrose) [2]
Fluorose (Fluoridvergiftung) [3]
Osteoblastische Metastase bei Mamma-Ca
Histiozytose [4]
Tuberöse Sklerose [5]
Östrogentherapie [6]
Hypoparathyreoidismus [7]
Therapie mit Romosozumab [8]
Therapie mit *rhPTH 1-84* [9]
Osteopetrose [10]
Osteom oder Osteosarkom
Morbus Paget [11]
Melorheostose/Léri-Syndrom [12]

Auflösung: Postoperativer Hypoparathyreoidismus mit Parathormonersatztherapie

Frau J. entwickelte bereits kurz nach der Operation eine ausgeprägte Hypokalzämie, die initial mittels Kalziumtabletten therapiert wurde. Ihre Symptome persistierten jedoch und umfassten Parästhesien, Fatigue, Brain Fog, Konzentrations- und Gedächtnisstörungen und verschlechterten sich im Verlauf deutlich. Nach einem halben Jahr befanden sich ihre Hände täglich 6 bis 8 h in Pfötchenstellung. Erst nach Vorstellung beim Hausarzt und Bestimmung des Parathormons wurde die Diagnose eines Hypoparathyreoidismus gestellt. Nach einjähriger unzureichender Standardtherapie wurde eine Parathormonersatztherapie eingeleitet, woraufhin sich die Symptome und Lebensqualität deutlich besserten. Zum Zeitpunkt der Knochendichtemessung war die Therapie mit rhPTH (1-84) bereits eineinhalb Jahre erfolgt. Die hohe Knochendichte erklärt sich durch die Kombination aus Hypoparathyreoidismus, Therapie mit rhPTH (1-84) und Übergewicht. Mögliche Differenzialdiagnosen einer Zunahme der Knochendichte sind im Nachfolgenden aufgelistet (◘ Tab. 1).

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Einhaltung ethischer Richtlinien

Interessenkonflikt. S. Geiger und K. Amrein geben an, dass kein Interessenkonflikt besteht.

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Hinweis des Verlags. Der Verlag bleibt in Hinblick auf geografische Zuordnungen und Gebietsbezeichnungen in veröffentlichten Karten und Institutsadressen neutral.

REFERAT

ENDOKRINOLOGIE

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Ursachen, Diagnose und Therapie

Hypoparathyreoidismus auf den Punkt gebracht

Der Hypoparathyreoidismus ist eine seltene Erkrankung im Bereich der inneren Medizin und oft ein wahres Chamäleon. Mögliche Symptome reichen von Parästhesien, Fatigue und Konzentrationsschwierigkeiten über Tetanien und Epilepsien bis hin zu lebensbedrohlichen Arrhythmien und Laryngospasmen. In manchen Fällen kann die korrekte Diagnosestellung Jahre dauern.[1-4]

KEYPOINTS

- *Auslöser des Hypoparathyreoidismus ist ein Parathormonmangel. Oft tritt dieser als Komplikation einer Halsoperation (Schilddrüsen-Op) auf.*
- *Häufige Symptome sind neuromuskuläre Störungen, wie Krämpfe, Tetanien, Parästhesien und Myalgien.*
- *Die Erkrankung ist psychisch, physisch und emotional belastend. Permanente Fatigue, Brain Fog, Energielosigkeit und Konzentrationsschwierigkeiten führen oft zu einer erheblichen Reduktion der Lebensqualität.*
- *Diagnostik: Hypoparathyreoidismus ist wahrscheinlich, wenn bei niedrigem albuminkorrigiertem oder freiem Kalzium das Parathormon (PTH) unangemessen niedrig oder nicht nachweisbar ist, und bei normal-niedrigen PTH-Werten unter Hypokalzämie.*
- *Die konventionelle Therapie besteht aus oraler Kalzium- und aktiver/nativer Vitamin-D-Supplementation. Bei Therapieversagen oder Persistieren von Symptomen trotz ausgeschöpfter Therapie sollte rekombinantes humanes Parathormon (1-84) als Zusatz in Betracht gezogen werden.*

Im folgenden Artikel geben wir einen kurzen Überblick über Ursachen, Diagnose und Therapie der Erkrankung (Tab. 1).

Ursachen

Auslöser des Hypoparathyreoidismus ist ein Mangel an Parathormon (PTH), der bei 75 % der Patienten als Komplikation einer Halsoperation, meist in der Folge einer Schilddrüsenoperation, auftritt. Wenn dieser Mangel kürzer als 6 Monate nach Operation besteht, spricht man von einem transienten, bei längerer Dauer von einem chronischen Hypoparathyreoidismus.[5]

Seltenere Ursachen sind autoimmune oder genetische Störungen.[5] PTH wird in den Nebenschilddrüsen produziert und ist ein wichtiger Regulator im Kalzium- und Phosphathaushalt. Es steuert die renale Reabsorption dieser Elektrolyte, stimuliert die Bildung von 1,25-Dihydroxyvitamin D (Vitamin D) und fördert den Knochenumbau durch Aktivierung von Osteoblasten und Osteoklasten.[6] Durch den Mangel an PTH kommt es zu Hypokalzämie, Hyperphosphatämie und erhöhter Kalziumausscheidung im Harn.[1,2]

Symptome und Folgen der Erkrankung

Das klinische Bild des Hypoparathyreoidismus wird meist durch einen zu niedrigen Kalziumspiegel verursacht, aber auch ein zu rascher Abfall des Serum-Kalziums im Normalbereich kann zu schwerwiegenden Symptomen führen.[3] Am häufigsten sind neuromuskuläre Störungen, wie Krämpfe, Tetanien, Parästhesien und Myalgien.[7] Neurologische Störungen umfassen ein erhöhtes Risiko für epileptische Anfälle, in selteneren Fällen Parkinsonismus, extrapyramidale Symptome, Dysarthrie und Ataxie, wobei die zugrunde liegenden Mechanismen unklar sind. Patienten mit Hypoparathyreoidismus zeigen auch eine erhöhte Prävalenz an intrazerebralen Verkalkungen, vor allem im Bereich der Basalganglien, wobei die klinische Relevanz dieser Verkalkungen noch zur Diskussion steht. Zu den kardiovaskulären Symptomen zählen QT-Verlängerungen, Bradykardien und Arrhythmien bis Torsades de pointes.[1–3]

Bei nicht operativ verursachtem Hypoparathyreoidismus kann es zusätzlich zu einer Verbreiterung der Intima und Media in den Gefäßen kommen, was in der Folge zu einem erhöhten Risiko für kardiovaskuläre Erkrankungen führt.[8,9]

Auch das Risiko für Nierenerkrankungen wie Nephrokalzinose, Nierensteine und eingeschränkte Nierenfunktion ist deutlich erhöht.[1,2] So zeigte sich in Kohortenstudien eine deutliche Reduktion der renalen Filtrationsrate im Vergleich zur Normalbevölkerung, wobei 29 % der Patienten eine eGFR von unter 60 ml/min/1,73 m^2 hatten.[10]

Im Knochen kommt es durch den Mangel an PTH zu einer Verlangsamung des Umbaus und zu einer Zunahme der Knochendichte, wobei die Auswirkungen auf das Frakturrisiko noch unklar sind.[11] Neuere Forschungsergebnisse fanden bei Patienten mit Hypoparathyreoidismus trotz erhöhter Knochendichte vermehrt Wirbelkörperfrakturen, die am häufigsten bei postmenopausalen Frauen und Patienten mit antikonvulsiver Therapie gefunden wurden.[12,13]

Zu dem breiten Spektrum an weiteren Symptomen zählen außerdem ein deut-

lich erhöhtes Risiko für Katarakte, dermatologische Erkrankungen wie trockene Haut und Alopezie und eine höhere Infektanfälligkeit.[2, 14, 15] In zwei Studien konnte auch eine erhöhte Mortalität demonstriert werden.[14, 16]

Für viele Patienten ist die Erkrankung aber vor allem eine psychische, physische und emotionale Belastung. Trotz adäquater Therapie können permanente Fatigue, Brain Fog, Energielosigkeit und Konzentrationsschwierigkeiten bestehen und zu einer erheblichen Reduktion der Lebensqualität führen, die häufig vom medizinischen Personal und von Nichtbetroffenen unterschätzt wird. Mehrere Studien belegten ein erhöhtes Risiko für psychische Erkrankungen wie Depressionen und Angststörungen.[17, 18]

Diagnose

Akute und chronische Hypokalzämien sollten, ob symptomatisch oder asymptomatisch, immer abgeklärt werden. Wichtig ist es, das albuminkorrigierte Kalzium zu errechnen, oder, wenn möglich, direkt das freie Kalzium zu messen.[2, 19] Ist das Serum-Kalzium erniedrigt, sollten, neben einer gründlichen Anamnese, zusätzlich Phosphat, Magnesium, PTH, Vitamin-D-Metaboliten und die Nierenfunktion erhoben werden. Bei hohen Phosphatspiegeln verbindet sich dieses mit Kalzium zu Kalziumphosphatkristallen, fällt aus und kann so eine Hypokalzämie verursachen. Hypo- und Hypermagnesiämie können die PTH-Sekretion unterdrücken und somit funktionell den Kalziumspiegel senken.[20] Eine eingeschränkte Nierenfunktion kann aufgrund reduzierter Reabsorption zu einer Hypokalzämie führen, wobei folglich das PTH oft im Rahmen eines sekundären Hyperparathyreoidismus erhöht ist.[19]

Die Diagnose eines Hypoparathyreoidismus kann nach Ausschluss anderer Ursachen gestellt werden, wenn bei niedrigem albuminkorrigiertem oder freiem

Tabelle	
Ursachen	• meistens postoperativ • genetisch (z. B. AIRE, CaSR, DiGeorge-Syndrom) • autoimmun • idiopathisch
Symptome	buntes Bild, u. a. • Krämpfe, Tetanien, Parästhesien und Myalgien, epileptische Anfälle • reduzierte psychische und physische Leistungs- und auch Arbeitsfähigkeit • kardiovaskuläre Manifestationen • Fatigue, depressive Verstimmung, Angststörungen
Langfristige Komplikationen	u. a. • Nierenerkrankungen • Infektionen • neuropsychiatrische Erkrankungen • erhöhte Mortalität
Diagnose	• Hypokalzämie und • niedriges oder normal-niedriges Parathormon • (Cave: bei Behandlung mit Kalziumsupplementierung oder hoher Kalziumzufuhr mit der Ernährung kann das Kalzium normal sein.)
Therapie	• Kalzium (Zufuhr >1000 mg, Optimierung der Ernährung, meist auch Supplemente erforderlich), cave: Dosierung nicht zu hoch wählen (max. 2–3 g/Tag) • Aktives Vitamin D (z. B. Calcitriol oder Alphacalcidol) • Natives Vitamin D (z. B. 2000 IU Vitamin D3 tgl., zumindest im Winterhalbjahr) • rhPTH (1-84) in besonders schweren Fällen
Kontrollen	• bei stabilem Verlauf 6-monatlich • nach Änderung der Therapie kurzfristig, Labor nach 1–2 Wochen
Sonderfälle	• Schwangerschaft bei Hypoparathyoidismus ist möglich, erfordert aber ein enges interdisziplinäres Management und engmaschige Betreuung des Neugeborenen. • Nach bariatrischen Operationen oder anderen Ursachen einer Malabsorption kann das Management eines Hypoparathyroidismus sehr schwierig sein.
Cave	Iatrogene hyperkalzäme Episoden können rasch zu einer Verschlechterung der Nierenfunktion führen.

Tab. 1: Wichtige Punkte bei Hypoparathyreoidismus

Kalzium das PTH unangemessen niedrig oder nicht nachweisbar ist.[1] Ebenso kann bei normal-niedrigen PTH-Werten unter Hypokalzämie von einem Hypoparathyreoidismus ausgegangen werden, da das Parathormon unter diesen Bedingungen erhöht sein sollte. Zusätzlich wegweisend kann der aktive Vitamin-D-Spiegel sein, der aufgrund des PTH-Mangels meist erniedrigt ist.[2, 19]

Therapie

Die konventionelle Therapie bei Hypoparathyreoidismus besteht aus oraler Kalzium- und aktiver/nativer Vitamin-D-Supplementation. Das Ziel ist es, schwere Hypo- und Hyperkalzämien sowie Langzeitkomplikationen zu vermeiden. Zur ausreichenden Therapie sollte ein normal-niedriger Kalziumspiegel (8,0–8,5 mg/dl; 2,0–2,12 mmol/l) angestrebt werden.[1,2,21] Weitere Ziele sind das Vermeiden von therapiebedingten Hyperkalzämien und ein Kalzium-Phosphat-Produkt von unter 55mg^2/dl^2.[21]

Empfohlen wird eine über den Tag verteilte orale Kalziumsupplementation von 1 bis 2 g oder alternativ eine ausreichende Zufuhr über die Ernährung. Da die Kalziumabsorption im Darm mit anderen Medikamenten, wie zum Beispiel Levothyroxin, konkurrieren kann, sollte Patienten geraten werden, diese nicht gleichzeitig einzunehmen.[2,21] Aktives Vitamin D wird meist als Calcitriol oder Alfacalcidol verabreicht. Dosierungen bei Calcitriol liegen zwischen 0,5 und 1,5 µg pro Tag und in etwa beim Doppelten bei Alfacalcidol.[21] Regelmäßige Kontrollen der Serum-Elektrolyte und des Harn-Kalziums sowie individuelle Anpassungen der Therapie sind notwendig, um eine effektive Therapie zu gewährleisten.[21,22] Bei einer Kalziumausscheidung von über 300 mg/d im 24-h-Harn können Thiaziddiuretika verabreicht werden, um das Risiko für Hypokalzämien und Nierensteine zu senken.[23] Probleme der konventionellen Therapie sind teilweise sehr hohe tägliche Kalziumeinnahmen mit gastrointestinalen Nebenwirkungen oder iatrogene Hyperkalzämien.[23]

Rekombinantes humanes Parathormon (1-84), rhPTH (1-84), ist seit 2017 in Europa als Hormonersatztherapie bei Hypoparathyreoidismus zugelassen. Bei Versagen der konventionellen Therapie oder Persistieren von Symptomen trotz ausgeschöpfter Therapie sollte rhPTH (1-84) als Zusatz in Betracht gezogen werden.[22] In randomisierten Kontrollstudien konnten bei einem Großteil der Patienten mit rhPTH (1-84) die Dosierungen von Kalzium und Vitamin D um mehr als die Hälfte reduziert werden, das Harn-Kalzium konnte gesenkt werden.[23,24] In Studien zur Verbesserung der Lebensqualität unter Hormonersatztherapie scheint sich die Lebensqualität im Vergleich zur konventionellen Therapie zu verbessern, jedoch sind die Studienergebnisse dazu noch nicht eindeutig, einzelne Fälle mit schwerem Hypoparathyreoidismus zeigten aber teilweise dramatische Verbesserungen.[17,25] ■

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■13

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5.8 Infoblatt / Factsheet

Hypoparathyreoidismus

Retrospektive Beobachtungsstudie 2021

Diplomarbeit von Simon Geiger

Bei der **Nebenschilddrüsenunterfunktion** (Hypoparathyreoidismus) kommt es zu einer zu niedrigen Ausschüttung von **Parathormon** (PTH). Nachfolgend eine kurze Zusammenfassung der Erkrankung:

PTH ⬇

Bei weniger PTH kann weniger Kalzium in den Knochen ein- und ausgebaut werden.

Im Darm wird bei weniger PTH weniger Kalzium aufgenommen.

In der Niere wird bei weniger PTH weniger Vitamin D gebildet und mehr Kalzium im Harn ausgeschieden.

Kalzium ⬇

Dadurch kommt es beim Hypoparathyreoidismus zu **Hypokalzämien**.

Symptome

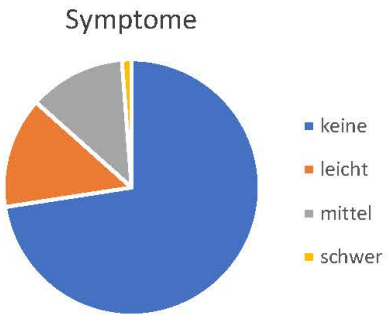
- Muskelkrämpfe
- Herzrhythmusstörungen
- Missempfindungen der Haut
- Selten Epilepsie

Therapie

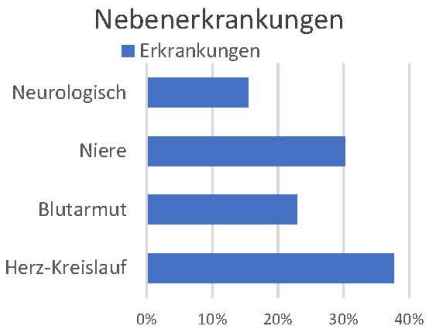
- Tägliche Einnahme von Kalzium und aktivem Vitamin D.
- Falls Kalzium und aktives Vitamin D nicht ausreichen kann rekombinantes humanes Parathormon (1-84) 1x täglich subkutan gespritzt werden.

Studie

In dieser Studie analysierten wir die medizinischen Daten von 191 PatientInnen mit Hypoparathyreoidismus. 70% unserer Studiengruppe waren weiblich, 82% hatten einen postoperativen Hypoparathyreoidismus und das mittlere Alter war 62 Jahre.



27% aller Patienten hatten Symptome trotz bestehender Therapie. Am häufigsten waren Parästhesien, Tetanien und Fatigue.



90% aller Patientinnen hatten Nebenerkrankungen. Am häufigsten waren Herz-Kreislauf-Erkrankungen, Anämien und Nierenerkrankungen.

Zusammenfassung

Viele PatientInnen mit Hypoparathyreoidismus haben trotz bestehender Therapie Symptome. Außerdem fanden wir bei 42% der PatientInnen eine eingeschränkte Nierenfunktion. Diese Komplikation ist eine bekannte Langzeitfolge von chronischem Hypoparathyreoidismus. Nierenprobleme können Herz-Kreislauf Erkrankungen verursachen und die Lebensqualität weiter beeinträchtigen. Wir fanden in dieser Studie zusätzlich eine auffällig hohe Rate an Blutarmut, die bisher nicht in der wissenschaftlicher Literatur beschrieben wurde.
Die Vorbeugung und Behandlung dieser Langzeitfolgen werden in Zukunft höchstwahrscheinlich wichtige Forschungsbereiche darstellen, da viele der zugrundeliegenden Mechanismen noch unbekannt sind.

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