Diplomarbeit

Hypoparathyroidism – renal and skeletal manifestations

eingereicht von

Johanna Windisch

zur Erlangung des akademischen Grades

Doktorin der gesamten Heilkunde

(Dr. med. univ.)

an der

Medizinischen Universität Graz

ausgeführt am

Universitätsklinikum für Innere Medizin

Klinischen Abteilung für Endokrinologie und Diabetologie

unter der Anleitung von

Priv.-Doz.^{in} Dr.^{in}med.univ Karin Amrein, MSc

Dr.^{in} med.univ. Adelina Tmava

Graz, am 04.03.2022

Eidesstattliche Erklärung

Ich erkläre ehrenwörtlich, dass ich die vorliegende Arbeit selbstständig und ohne fremde Hilfe verfasst habe, andere als die angegebenen Quellen nicht verwendet habe und die den benutzten Quellen wörtlich oder inhaltlich entnommenen Stellen als solche kenntlich gemacht habe.

Graz, am 04.03.2022 Johanna Windisch eh

Acknowledgments

First and foremost, I would like to thank Karin Amrein for her amazing support during the process of writing this thesis. She guided me the whole time with tireless commitment and knowledge and motivated me always to dig a little bit deeper.

I furthermore want to thank Theresa Lerchl and Simon Geiger that analysed the patient data with me. I think, we made an excellent team.

I would like to extend my thanks to Gerit Wünsch of the Institute of Medical Informatics, Statistics and Documentation of the Medical University of Graz. Without her help in data retrieval, none of this would have been possible.

Lastly, I want to thank my family, especially my parents and brother, and my partner Thomas for always supporting me.

Contents

Abbreviations

aBMD	areal BMD
aHR	adujsted hazard ratio
APS 1	autoimmune polyendocrine syndrome 1
BAP	bone-specific alkaline phosphatase
BMD	bone mineral density
BMSi	bone material strength index
CaSR	calcium sensing receptor
CI	confidence interval
CKD	chronic kidney disease
Ct.vBMD	cortical volumetric bone mineral density
CTAL	cortical thick ascending limbs of the loop of Henle
CTX	cross-linked C-telopeptide of type 1 collagen
DCT	distal convoluted tubule
DXA	dual energy X-ray absorptiometry
eGFR	estimated glomerular filtration rate
FEPh	fractional excretion of phosphate
hcu	hypercalciuria
Hp	hyperphosphatemia
HR	hazard ratio
hyperPT	hyperparathyroidism
hypoPT	hypoparathyroidism
iPTH	intact PTH
IQR	interquartile range
NC	nephrocalcinosis
ng	not given
nHCE	number of hypercalcaemic episodes
NL	nephrolithiasis
nshypoPT	nonsurgical hypoPT
NXCX1	sodium/calcium exchanger 1
OR	odds ratio
P1NP	procollagen type 1 amino-terminal propeptide
post	postmenopausal
pQCT	peripheral quantitative computed tomography
pre	premenopausal
pshypoPT	postsurgical hypoPT
PTH	parathyroid hormone
PTH1R	PTH/PTHrP receptor type 1
PTH2R	PTH receptor type 2
rHc	relative hypercalcaemia
rhPTH	recombinant human parathyroid hormone
sCa	serum calcium
sCaxP	serum calcium phosphate product
sP	serum phosphate

Tb.vBMD	trabecular volumetric bone mineral density
TBS	trabecular bone score
TRPV6	transient receptor potential cation channel subfamily V member 6
uCa	urinary calcium
vBMD	volumetric bone mineral density
VF	vertebral fracture

Figures

Tables

Zusammenfassung

Hintergrund

Hypoparathyreoidismus (HypoPT) ist ein zweifaches Hormonmangelsyndrom: Parathormon (PTH) und aktives Vitamin D sind vermindert. Verletzung, Entfernung oder genetische Defekte der Nebenschilddrüse führen zu chronisch niedrigen PTH-Werten und damit zu Hypokalzämie und Hyperphosphatämie. HypoPT kann sich in vielen Organsystemen manifestieren, vor allem in Niere und Knochen, die in dieser Arbeit analysiert wurden. Es ist die letzte Endokrinopathie, die nicht standardmäßig mit dem fehlenden Hormon therapiert wird.

Methoden

Diese retrospektive Beobachtungsstudie inkludiert Patient*innen mit chronischem postoperativen (psHypoPT) und nicht-operativen HypoPT (nsHypoPT), die an der Medizinischen Universität Graz behandelt wurden. Sie wurden mittels openMEDOCS identifiziert. Einschlusskriterien waren PTH-Werte unter 30pg/mL und Hypokalzämie. Der Effekt auf Niere und Knochen wurde untersucht und eine Literaturrecherche durchgeführt.

Resultate

191 Patient*innen wurden identifiziert, 156 mit psHypoPT und 35 mit nsHypoPT. Die durchschnittliche Erkrankungsdauer war 9,1 Jahre. 11 Patient*innen bekamen eine rhPTH Therapie. Das Durchschnittsalter war 61.7 Jahre, Patient*innen mit psHypoPT waren älter als jene mit nsHypoPT (Durchschnittsalter 64,7 vs. 48,5 Jahre, $p<0,001$). 70% waren Frauen. Sie hatten ein größeres Risiko für psHypoPT als für nsHypoPT (86,5% vs. 70,7% $p=0,01$; OR 2.65).

Die Nierenfunktion war leicht eingeschränkt (durchschnittliche eGFR 61,2 mL/min/1,7m^2) und die eGFR von Patient*innen mit psHypoPT war niedriger als von jenen mit nsHypoPT (59,1 vs 72,8 mL/min/1,7m^2, $p=0,02$). Renale Verkalkungen waren häufiger bei nsHypoPT als bei psHypoPT (17,1% vs. 5,1%, $p=0,025$, OR 3,83).

Auch Frakturen waren häufiger bei Patient*innen mit nsHypoPT (28,6% vs. 12,2%, $p=0,33$; OR 2,88), vor allem am Femurhals und der unteren Extremität (11,4% vs.

0,6% p=0,004 und 17,1% vs. 3,2% p=0,006). Insgesamt waren 53 Frakturen für die Kohorte dokumentiert. Der Durchschnitt des T-Score war 0,75 (Lendenwirbelsäule) and 0,13 (Femurhals). Es gab keinen Unterschied zwischen beiden Gruppen.

Conclusio

Chronischer Hypoparathyreoidismus ist eine komplexe Erkrankung, die eine große Bandbreite an Symptomen aufweist. Unsere retrospektive Beobachtungsstudie, an einem großen tertiären Zentrum, mit 156 psHypoPT und 35 nsHypoPT Patient*innen, konnten viele renale und skelettale Morbiditäten erfassen. Diese waren besonders ausgeprägt in der Gruppe mit nsHypoPT, obwohl diese jünger war. Weitere Studien sind notwendig, um die Therapie zu optimieren und das Risiko für Nebenwirkungen zu vermindern.

Abstract

Background

Hypoparathyroidism (hypoPT) is a two-hormone deficiency syndrome: parathyroid hormone (PTH) and active vitamin D are reduced. Damage, removal, or genetic defects of parathyroid glands cause chronically low PTH levels and consequently hypocalcaemia and hyperphosphatemia. HypoPT can manifest in many organ systems, especially kidney and bone that are studied in this thesis. It remains the last endocrinopathy that is not usually treated with the lacking hormone.

Methods

This retrospective observational study included patients with chronic postsurgical hypoPT (pshypoPT) and nonsurgical hypoPT (nshypoPT), treated at the Medical University of Graz. Patients were identified via openMEDOCS and included with PTH levels below 30pg/mL and hypocalcaemia. Renal and skeletal outcomes were assessed. Furthermore, a literature research was conducted.

Results

191 patients were identified, 156 pshypoPT and 35 nshypoPT. Mean disease duration was 9.1 years. 11 patients received rhPTH 1-84 replacement therapy. The mean age was 61.7 years, patients with pshypoPT were older compared to nshypoPT (mean 64.7 vs. 48.5 years, $p<0.001$). 70% were women. They were more likely to have pshypoPT than nshypoPT (86.5% vs. 70.7% $p=0.01$, OR 2.65).

Kidney function was slightly impaired (mean eGFR 61.2 mL/min/1.7m^2) and patients with pshypoPT had significantly lower eGFR than those with nshypoPT (59.1 vs 72.8 mL/min/1.7m^2, $p=0.02$). Renal calcification was documented more often in patients with nshypoPT compared to pshypoPT (17.1% vs. 5.1%, $p=0.025$, OR 3.83).

Despite younger age, more patients with nshypoPT had a history of fractures (28.6% vs. 12.2%, $p=0.33$, OR 2.88), specifically, femur and other lower extremity fractures (11.4% vs. 0.6% $p=0.004$ and 17.1% vs. 3.2% $p=0.006$ respectively). Overall, 53 fractures were documented for the cohort.

Mean T Scores were 0.75 (lumbar spine) and 0.13 (proximal femur). They did not differ between both groups.

Conclusion

Chronic hypoPT is a complex disease that can present with a variety of symptoms and complications. In our retrospective observational study of a tertiary center including 156 pshypoPT and 35 nshypoPT, we found a high renal and skeletal morbidity, particularly in nshypoPT. Further studies are required to optimize treatment and lower the risk for adverse outcomes in these patients.

1 Introduction

1.1 Physiology of PTH

Parathyroid hormone (PTH) is a peptide hormone that is synthesised in the parathyroid glands. It regulates calcium and phosphate homeostasis. Its main effect is the rapid increase in serum calcium. This is achieved directly by an augmented calcium reabsorption and decreased phosphate uptake in the kidney and an increase in bone resorption, as well as indirectly through stimulation of vitamin D synthesis in the kidney (1).

1.1.1 Synthesis and secretion of PTH

PTH is encoded in chromosome 11. Via preproPTH, consisting of 115 amino acids, the final hormone PTH(1-84), containing 84 amino acids, is produced and then secreted. Through the blood it reaches its main target organs, kidney and bone. The plasma half-life of endogenous PTH is only a few minutes.

The production of PTH is mainly regulated by the level of ionized calcium in the extracellular fluid (ECF Ca^{++}) which is detected by the calcium sensing receptor (CaSR). Ca^{++} binding to this receptor inhibits the secretion of PTH. Additionally, it may result in the depletion of bioactive PTH within the cells of the parathyroid glands. Low plasma Ca^{++} levels lead to an increase in PTH secretion and proliferation of parathyroid cells.

Other regulators of PTH secretion are $1,25(OH)_2D$, the active form of vitamin D, and fibroblast growth factor 23 (FGF23). $1,25(OH)_2D$ is the ligand of the vitamin D receptor (VDR) on the parathyroid cells. It prevents gene transcription of PTH (similar to high calcium levels) and may upregulate CaSR, again resulting in a decrease PTH secretion (1). FGF23, a proteohormone produced by osteocytes with phosphaturic effects on the kidney (2), also inhibits PTH secretion.

Inactive PTH fragments are excreted by the kidney. As the renal clearance is rather slow compared to the short plasma half-life in a physiological state, only 20% of the circulating PTH is the biologically active version PTH(1-84).

The amino (NH_2)-terminal domain of PTH binds to the receptors and is responsible for the biological activity of the hormone. The most important one is the PTH/PTHrP receptor type 1 (PTH1R), a G-protein-coupled receptor. It is abundant in kidney and bone, the main target organs of PTH, but can also be found in various other tissues. It activates various pathways, the most important ones are the adenylate cyclase (AC) pathway, causing an increase of cAMP, and the phospholipase C (PLC) pathway, resulting in the release of calcium from the endoplasmatic reticulum (1).

PTH also binds to the PTH receptor type 2 (PTH2R). It is expressed all over the body, but mainly in the nervous system. It plays an important role in wound healing, nociception and maternal behaviour, and influences calcium transport and keratinocyte differentiation Additionally, tuberoinfundibular peptide of 39 residues (TIP39) and PTHrP are ligands of this receptor (3).

PTH does not only have an effect on the main target organs, kidney and bone that will be discussed in the following, but can also influence insulin sensitivity, lipolysis and cardiovascular disease (4).

1.1.2 Effect of PTH on kidney

In the kidney, PTH leads to an increase in calcium and magnesium resorption, the inhibition of phosphate and bicarbonate reuptake and a stimulation of $1,25(OH)_2D$ production. This happens faster than the reaction to PTH in bone.

The majority of calcium is reabsorbed paracellularly in the proximal tubulus, in combination with sodium and water. PTH can only influence the calcium reabsorption in the distal nephron, including the cortical thick ascending limbs of the loop of Henle (CTAL), distal convoluted tubule (DCT) and possibly connecting tubules. In the CTAL, the interaction of PTH and the PTH1R stimulates the activity of the Na/K/2Cl cotransporter, which in turn generates a gradient that leads to paracellular resorption of calcium via paracellin.

CaSR is also present in these tubule cells and can counteract this effect if the calcium in the extracellular fluid is too high. In the DCT, the reabsorption happens actively through the transient receptor potential cation channel subfamily V member 6 (TRPV6), followed by translocation through the cell with calbindin and transportation into the blood by sodium/calcium exchanger 1 (NXCX1) (1). PTH enhances the expression of these 3 proteins, increasing calcium reabsorption(5). This is illustrated in **Figure 1**.

Phosphate resorption is inhibited if PTH binds to the PTH1R on the cells of the proximal tubule. This leads to the removal of the two sodium-dependent cotransporters for phosphate (NaPi-IIa and NaPi-IIc) from the brush border membrane that are responsible for the uptake of phosphate into tubule cells. They are internalised via clathrin-coated pits and subsequently degraded in the lysosomes. In this process, certain pathways are activated and cAMP is generated, which is then excreted in urine, where it can be detected and serves as a way to monitor PTH function (1).

It must be noted, that through the elevation of plasma calcium levels induced by PTH, the net excretion of calcium also increases, diminishing the total calcium of the body. Therefore, PTH activates the last step of $1,25(OH)_2D$ synthesis in the kidney. This hormone stimulates the uptake of calcium and phosphate in the gastrointestinal tract, countering the loss of calcium and phosphate (2).

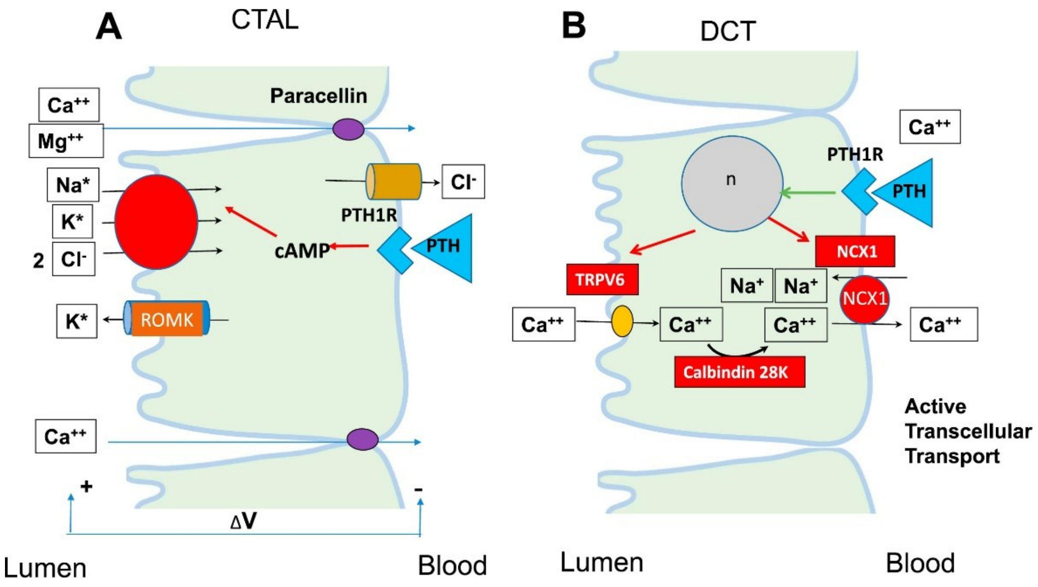


__Figure 1__: PTH regulates calcium reabsorption in kidney. A in the cortical thick ascending limb of the loop of Henle, B in the distal convoluted tubule (1).
Reprinted from Endocrinol Metab Clin North Am, 47 / 4, David Goltzman, Physiology of Parathyroid Hormone / Parathyroid hormone actions in kidney in regulating ion transport, 743-758., Copyright (2018), with permission from Elsevier. (https://www.sciencedirect.com/journal/endocrinology-and-metabolism-clinics-of-north-america)

1.1.3 Effect of PTH on bone

PTH binds to the PTH1R on osteoblasts and osteocytes and can have an anabolic or catabolic effect on bone, depending on the duration and periodicity of the exposure (6).

The **catabolic effect** of PTH is mainly due to its effect on the RANK/RANKL system and leads to the desired increase in calcium and phosphate (1). As those two substances share a solubility equilibrium, this process alone does not augment the biological active calcium. The additional action of the kidney (decrease of phosphate, increase in calcium) is needed to actually increase the ionized calcium available (2).

PTH increases the expression of RANKL on osteoblasts (1), which is the ligand to the RANK receptor on precursor cells of osteoclasts. The interaction of RANKL and RANK leads to the differentiation, fusion and activation of osteoclasts and their progenitors, therefore resulting in increased bone resorption. Additionally, the production of osteoprotegerin (OPG), a glycoprotein that prevents this interaction as a decoy receptor, is inhibited, furthermore increasing the bone resorption (6).

It seems, that PTH affects cortical and trabecular bone differently, with a tendency to degrade the former and spare the latter. Additionally, there is evidence, that PTH is needed for normal trabecular structure and quantity (1).

The **anabolic effect** is seen in intermittent exposure to PTH. An early phase of bone formation is followed by a general increase in bone turn-over. This so called “anabolic window” is used in therapy for osteoporosis. Osteoblast proliferation and differentiation is stimulated and apoptosis is reduced by PTH. For example, it inhibits the production of sclerostin in the osteocytes, a glycoprotein that is a negative regulator of bone formation (6) .This effect seems to dominate in trabecular bone (1).

In conclusion, PTH is essential for normal skeletal physiology and bone turnover (6).

1.2 Pathophysiology of hypoparathyroidism

In hypoparathyroidism (hypoPT) the effect of PTH is reduced or absent, because of a lack of the hormone itself. This leads to a reduction of calcium conservation in the kidney, which induces relative hypercalciuria compared to serum calcium levels. Additionally, hyperphosphatemia occurs, because the phosphaturic effect of PTH is missing. Moreover, 1,25-dihydroxyvitamin D is decreased, and therefore calcium uptake in the gastrointestinal tract, is low, making hypoPT a two hormone deficiency syndrome. In bone, turnover is decreased and mobilisation of calcium and phosphate declines. This leads to chronic hypocalcaemia and hyperphosphatemia in combination with inappropriately low PTH levels (7). We talk about chronic hypoPT, when this condition lasts longer than 6 months (8).

1.3 Chronic manifestations of hypoparathyroidism

Chronic manifestations can be caused either by the disease itself, the therapy or a combination of both (9). The combination of PTH deficiency and the conventional therapy (high dose calcium supplements and active vitamin D) can lead to chronic hypocalcaemia with episodes of hypercalcaemia, resulting in an increased calcium phosphate product and hypercalciuria. An additional frequent issue is hyperphosphatemia. Many organs can be affected by this condition. Although it is clear, that complications in hypoparathyroidism are caused by disturbances in the calcium and phosphate homeostasis, the exact pathophysiological mechanism remains unknown (10,11).

1.4 Renal manifestation

In the absence of PTH, the kidney’s ability to reabsorb calcium is reduced, leading to hypercalciuria. Its severity depends on renal function and plasma calcium levels, which can be influenced by therapy (7). However, the pathophysiological mechanism of renal impairment in hypoPT remains unknown, as so far, no clear association of hypercalciuria with renal complications could be shown (12). The renal complications that were investigated most frequently are nephrolithiasis (NL), nephrocalcinosis (NC) and chronic kidney disease (CKD) (13). They seem to be related to conventional therapy (14), which is why this chapter focusses on renal manifestations under calcium and vitamin D treatment. The effect of PTH replacement therapy on the kidney will be discussed in chapter 1.6.

The systematic review by Gosmanova et al. describes the renal complications in patients treated with conventional therapy. They included papers published until November 2018 (13). Papers published after this date have been added in this thesis and together, they were analysed. **Table 1** gives an overview of study design and population of the studies.

Authors, year of publication (REF), study design	country	cases	controls	Aim
Arlt et al. 2002 (15) cross-sectional study	Germany	25 women with postsurgical hypoPT	25 age, sex and surgery matched controls	assess efficacy of calcium/vitamin D treatment
Astor et al. 2016 (16) survey using hospital registry	Norway	283 patients with chronic postsurgical (197), nonsurgical (70) and pseudo (16) hypoPT (overall: 75% women)	-	determine prevalence, aetiology, quality of life and treatment pattern of hypoPT
Bergenfelz et al. 2019 (9) retrospective observational study using national health registry	Sweden	239 subjects with postsurgical hypoPT after total thyroidectomy	4589 after total thyroidectomy, without permanent hypoPT (83% women)	evaluating risk of complications after total thyroidectomy with and without permanent hypoPT
David et al. 2019 (17) retrospective observational study	Belgium	143 patients with postsurgical and 16 patients with nonsurgical hypoPT	-	to determine complications in patients with chronic hypoPT
Gafni et al. 2018 (18) clinical trial	USA	31 patients with hypoPT (78% women)	-	assess effect of hPTH(1-34) (duration up to 5 years) on renal outcomes (baseline characteristics on conventional therapy were used here)
Hadker et al. 2014 (19) self reporting in cross-sectional survey	USA	374 patients with chronic hypoPT (85% women)	-	quantify clinical and social burden of illness for hypoPT
Ketteler et al. 2021 (20) retrospective cohort study	Germany	patients with hypoPT (8097 analysed for nephrolithiasis, 8051 for nephrocalcinosis; 76% women)	40485 randomly selected adults without hypoPT (54% women)	assess association of hypoPT with nephrolithiasis and calcinosis in a large cohort
Kim et al. 2015 (21) retrospective study	South Korea	37 pediatric patients with primary hypoPT (38% women)	-	assess clinical course and aetiology of primary hypoparathyroidism in infancy and childhood
Kim et al. 2020 (22) retrospective cohort study	South Korea	210 patients with nonsurgical hypoPT and no prior complications (59% women)	2075 age, sex and comorbid disease matched controls	estimate risk of complications in hypoPT
Leidig-Bruckner et al. 2016 (23) retrospective, longitudinal chart review	Germany	33 patients with medullary thyroid carcinoma and postsurgical hypoPT (55% women)	-	identification of factors influencing long-term outcome in complete or partial postoperative hypoparathyroidism in medullary thyroid carcinoma

Levy et al. 2015 (24) long-term retrospective follow-up study	Canada	29 paediatric patients with chronic hypoPT (48% girls)	-	assess impact of hypoparathyroidism treatment on renal function in children
Lopes et al. 2016 (25) retrospective observational study	Brazil	55 patients with chronic postsurgical (41), pseudo (5) and autoimmune (9) hypoPT (76% women)	-	determine prevalence and predictors for renal abnormalities in hypoPT
Meola et al. 2018 (26) prospective study	Italy	90 patients with postsurgical hypoPT (76% women)	142 healthy, sex- and age-matched controls	evaluation of adherence to European Society of Endocrinology guidelines and risk of renal complications in hypoPT
Mitchell et al. 2012 (27) retrospective, longitudinal chart review	USA	120 patients with chronic hypoPT (73% women)	-	characterization of course of disease in a large cohort of hypoparathyroid patients
Ochsner Ridder et al. 2021 (12) cross sectional study	Denmark	166 subjects with postsurgical (125) and nonsurgical (41) hypoPT (80% women)	-	assessing the association of hypercalciuria on renal morbidity in chronic hypoPT
Saha et al. 2020 (28) observational study in tertiary care center	India	165 patients with primary hypoPT on conventional therapy (45% women)	165 age- and sex-matched healthy individuals (used only for renal imaging)	assess the long-term safety of conventional therapy on renal health
Underbjerg et al. 2013 (29) retrospective study using national health registry	Denmark	688 subjects with postsurgical hypoPT (surgery for non-malignant cause) (88% women)	2064 age- and gender-matched individuals from general population	identify all people with postsurgical hypoPT in Denmark and evaluate their renal and cardiovascular complications
Underbjerg et al. 2015 (30) retrospective study using national health registry	Denmark	180 patients with nonsurgical hypoPT (53% women)	180 gender- and age-matched population-based control	identify all patients with nonsurgical hypoPT in Denmark and evaluate their risk of complication and mortality
Underbjerg et al. 2018 (11) retrospective case-control study	Denmark	patients with hypoPT and complications or deceased overall: 431 subjects with postsurgical and nonsurgical hypoPT (81% women)	hypoPT without complications	assessing association of biochemical parameters and risk of complications in chronic hypoPT
Vadiveloo et al. 2019 (31) retrospective population-based study	UK	280 subjects with hypoPT (69% women), subdivided into postsurgical (116), nonsurgical (106) and hypomagnesemia (58)	1301 age- and gender-matched individuals from general population	comparing mortality and morbidity of people with hypoPT to the general population

***Table 1**: Overview of studies on renal complications in hypoPT. author in cursive = analysed in systematic review by Gosmanova et al.* (13)*, hypoPT = hypoparathyroidism.*

1.4.1 Renal function

Impairment of renal function was investigated in 15 out of the 20 studies that were selected, however the definitions and therefore the reported rates varied between them. The terms renal failure, renal insufficiency, CKD stage 3 or higher and eGFR < 60 or 90mL/min/1.73m^2 were used to describe and define a compromised renal function. The obtained rates ranged from 0% (24) to 46% (25). Notably, the lowest rate, 0%, was in a study on children. Many of the low rates were obtained by identification of ICD codes (9,22,29,30), while 46%, the highest rate was observed, when renal impairment was defined as eGFR < 90mL/min (25). All studies using control groups found a significantly increased risk for compromised renal function in patients with hypoPT (9,22,29–31), with hazard ratios between 2.47 (31) and 9.39 (31). **Table 2** gives an overview of the different studies and results. **Figure 2** shows the rate of renal impairment of all studies.

Interestingly, Vadiveloo et al. observed a drop in the hazard ratio for renal failure 2000 days after baseline (first low calcium measured) in the nonsurgical group, from 7.59 to 1.63, with the latter not being significant anymore. This leads to an adjusted HR of 9.39 (CI 95% 5.58-15.78) within the first 2000 days for all patients with hypoparathyroidism, but only an adjusted HR of 2.47 (CI 95% 1.47-4.14) after this period (31).

Author, year of publication n=number of cases	term and definition	observed rate in cases (HR, CI 95%)	observed rate in controls
Astor et al. 2016 n=283	eGFR<60mL/min/1.73m^2	18%	-
Bergenfelz et al. 2019 n=239	renal insufficiency: ICD codes (not further specified)	2.5% (HR 4.88, 2.00-11.95)*	0.7%
Hadker et al. 2014 n=374	CKD reported as chronic kidney failure	17%	-
Kim et al. 2020 n=210	renal insufficiency: ICD-10 codes N18-N19	4.3% (aHR 3.44, 1.63-7.23)*	1.3%
Leidig-Bruckner et al. 2016 n=33	eGFR<60mL/min/1.73m^2	23%	-
Levy et al. 2015 n=29	eGFR<60mL/min/1.73m^2	0%	-
Lopes et al. 2016 n=55	CKD stage 2: eGFR<90mL/min/1.73m^2	46.7%	-
Meola et al. 2018 n=90	eGFR<60mL/min/1.73m^2	12.2%	-
Mitchell et al. 2012 n=120	eGFR<60mL/min/1.73m^2	41%	-
Ochsner Ridder et al. 2021 n=166	CKD stage 3 or higher: eGFR<60mL/min	18.3%	-

Saha et al. 2020 n=165	GFR<60mL/min/1.73m^2 (measured by plasma clearance of ^{99m}Tc-DTPA)	14.4%	-
Underbjerg et al. 2013 n=688	renal insufficiency: ICD-8 code 792.99 (uremia) or ICD-10 codes N18.0 to N18.9 (chronic renal insufficiency) or N19-N19.9 (renal insufficiency without specification)	5.1% (HR 4.95, 2.88-8.50)*	1.0%
Underbjerg et al. 2015 n=180	renal insufficiency: ICD-8 and ICD-10 codes (not further specified)	8.3% (HR 6.01, 2.45-14.75)*	1.5%
Underbjerg et al. 2018 n=431	renal insufficiency: eGFR<60mL/min	21%	-
Vadiveloo et al. 2019 (31) n=280	renal failure: eGFR<30mL/min	3.6% (aHR 9.39, 5.58-15.78 < 2000 days, aHR 2.47, 1.47-4.14 > 2000 days)*	0.8%

***Table 2**: Overview of studies assessing renal impairment. * = statistically significant (p-value<0.05), author in cursive = part of systematic review of Gosmanova et al.* (13)*, eGFR = estimated glomerular filtration rate, CKD = chronic kidney disease, HR=hazard ratio, aHR = adjusted hazard ratio CI = confidence interval.*

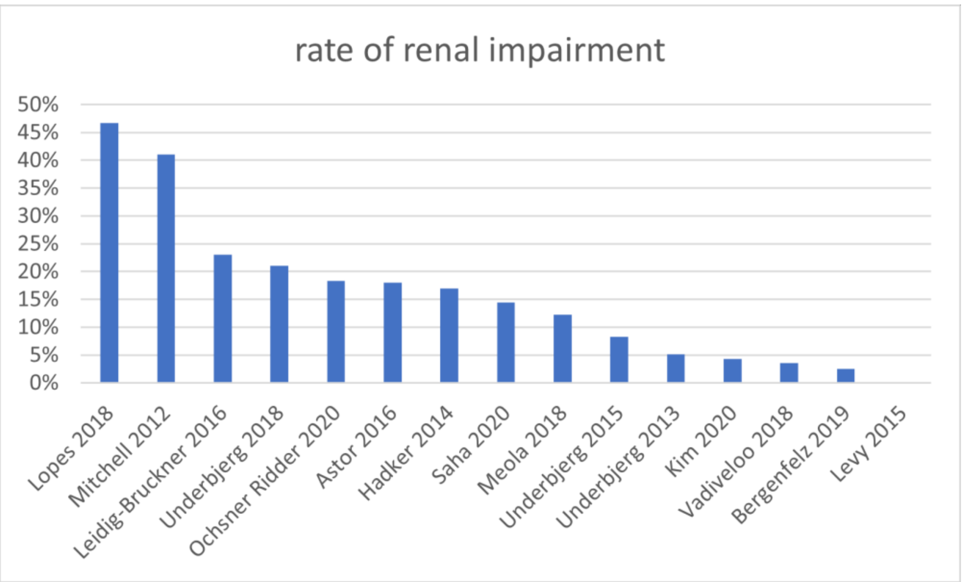


***Figure 2**: Rate of renal impairment in studies that were analysed.*

1.4.2 Renal calcification

The term renal calcification is used to describe nephrolithiasis or nephrocalcinosis. It was evaluated in 16 of the 20 selected studies. Again, definition and methods varied. There was a large variability in the percentage of patients with either nephrolithiasis, nephrocalcinosis or both with rates between 0% (24,26) and 48.8% (18). Hazard ratios ranged from 0.80 (30) to 6.94 (20).

Notably, the used methods were quite different between these studies, explaining at least partially the variability in renal calcification rates. Of the 6 studies using a control group, 5 found renal calcification to be significantly more common in hypoPT. **Table 3** gives an overview of the studies, methods, and rates of renal calcification.

The lowest rates (1.1% and 1.9%) were obtained by using ICD codes and in much larger cohorts than the other studies (29,30).

The high rate of 48.4% may be explained by the prospective study design and the small population. Before commencing hPTH(1-34) therapy, all 31 patients on conventional therapy were investigated by renal ultrasound and CT to determine baseline characteristics of renal calcification (18). Therefore, more asymptomatic patients were identified, which is not possible in the retrospective setting of the other studies.

Many of the high rates (12,21) were observed, when all patients with hypoPT and abdominal ultrasound or CT scans were analysed. This could have led to a selection bias as patients undergoing this examination are very likely to have had symptoms and therefore a much higher likelihood of renal calcification as those, who did not get renal imaging. This rate only shows the percentage among patients with hypoPT and abdominal imaging and not in hypoPT in general. The study by David et al. confirms this, as in the same cohort 14.7% of patients had a history of renal calcifications, but 21.8% of those with renal imaging had nephrolithiasis or nephrocalcinosis (17).

Given the methods that were used, the rates investigated by ICD codes may represent the percentage of symptomatic renal calcification, while studies using prospective renal imaging rather show the frequency in all patients.

author, year of publication n=number of cases	definition and methods	observed rate in cases (HR, CI 95%)	controls
Arlt et al. 2002 n=25	NL or NC: abdominal ultrasound performed at visit	8%	-
David et al. 2019 n=170	NL and/or NC: documented history of event positive results in renal imaging (n=87)	14.7% 21.8%	-
Gafni et al.2018 n=31	NC and/or NL: renal ultrasound and renal CT at baseline of hPTH(1-34) study (patients on conventional therapy)	48.4%	-
Hadker et al. 2014 n=374	NL: self-report	35.5%	
Ketteler et al. 2021 n=8097 (NL)/8051 (NC)	NL: ICD-9, ICD-10 and their Clinical Modification (CM) and Procedure Coding System (PCS), HCPS, CPT codes; NC: ICD-9-CM, ICD-10-CM	NL: aHR 1.81, 1.60-2.04*; NC: aHR 6.94, 4.41-10.92*	ng
Kim et al. 2015 n=26	NL or NC: retrospective analysis of patients with renal imaging	19.2%	-
Kim et al. 2020 n=210	renal stones: ICD-10 codes N20-N23 (stones in kidney and urethra, stones in lower urinary tract)	4.8% (aHR 2.13, 1.10-4.13)*	2.2%
Leidig-Bruckner et al. 2016 n=33	NL: retrospective analysis of radiological kidney imaging	30.8%	-
Levy et al. 2015 n=29	NL or NC: retrospective analysis of renal ultrasounds	NL: 0%; NC: 38%	-
Lopes et al. 2016 n=40	NL and NC: retrospective analysis of patients with renal ultrasound	25%	-
Meola et al. 2018 n=90	NL or NC: renal ultrasound performed at visit	NL: 30% (OR 8.2, 3.4-19-9)*; NC: 0%	5%
Mitchell et al. 2012 n=54	renal calcification (NL or NC): retrospective analysis of patients with renal imaging	31%	-
Ochsner Ridder et al. 2021 n=54	renal calcification (NL or NC): review of all patients with hypoPT at the department with abdominal imaging (ultrasound or CT)	renal calcification: 42.6%; isolated NC: 3.7%; isolated NL 18.5%; NL and NC: 24%	-
Saha et al. 2020 n=165	renal calcification (NC, NL): ultrasonography and radiograph	renal calcification: 11%; NC: 6.7%*; NL: 5.0%	NC: 0% NL: 3.6%
Underbjerg et al. 2013 n=688	renal stones: ICD-8 code for nephrolithiasis and ureterolithiasis; ICD-10 codes N20-N20.9 and N21-N23.9	1.9% (HR 4.82, 2.00-11.64)*	0.4%
Underbjerg et al. 2015 n=180	nephrolithiasis: ICD-8 and ICD-10 codes (not further specified)	1.1% (HR 0.80, 0.17-3.85)	1.3%

***Table 3**: Overview of studies investigating renal calcification, their methods, definitions and outcomes. * = statistically significant (p-value<0.05), author in cursive = previously analysed in systematic review by Gosmanova et al.* (13) *NC = nephrocalcinosis, NL = nephrolithiasis, HR = hazard ratio, aHR = adjusted hazard ratio, CI = confidence interval, ng=not given.*

1.4.3 Biochemical parameters

The association of biochemical parameters and renal disease was investigated in 7 of the 20 selected studies. **Table 4** gives an overview of the results (calcium, phosphate and urinary values).

High serum calcium was found to be directly associated with renal failure in one study (31) and with a lower eGFR in another (24). It furthermore showed a positive correlation with serum phosphate (25) and was directly associated with urinary calcium (27). The 3 other studies could not observe a link with serum calcium. The number of hypercalcaemic episodes was found to significantly increase the risk for any renal disease (11) and hypercalcemia was a significant predictor for nephrocalcinosis in children (24).

Two studies were able to show that a high serum calcium phosphate product was significantly associated with any renal disease (11) and a significant predictor for nephrocalcinosis (28). Contrary to that, another study found serum phosphate levels and serum calcium phosphate product to be inversely linked with renal calcification, with lower levels promoting calcification (12). Furthermore, hyperphosphatemia was found to be a direct predictor for nephrocalcinosis in children (24). Another study found no association between calcium phosphate product and eGFR (27).

The 4 studies that reported urinary calcium levels (hypercalcemia rates 20% (28) to 66% (12)) did not show a significant link with renal calcification or impaired renal function. These studies confirm previous analyses that were not able to link hypercalciuria to renal disease (13,15,26,27).

Nevertheless, as hypercalciuria is seen as a risk factor in euparathyroid subjects, and working under the presumption that renal calcification has a similar pathophysiology in both groups, it is recommended to keep the 24h urine calcium within the normal reference range (32).

author, year of publication n=number of participants studied outcome	association with calcium values: serum calcium (sCa), number of hypercalcaemic episodes (nHCE), relative hypercalcaemia (rHc)	association with phosphate values: serum phosphate (sP), hyperphosphatemia (Hp), serum calcium phosphate product (sCaxP)	association with urinary values: urinary calcium (uCa), fractional excretion of phosphate (FEPh) hypercalciuria (hcu): % of cases
Levy et al. 2015 n=29 nephrolithiasis serum calcium	sCa: indirect association with eGFR* nHCE: - rHc: direct predictor for nephrocalcinosis*	sP: - Hp: direct predictor for nephrocalcinosis* sCaxP: -	uCa: positive correlation with serum calcium FEPh: - hcu: -
Lopes et al. 2016 n=55 serum calcium, renal calcification	sCa: no association with uCa, positive correlation with sP* nHCE: - rHc: -	sP: positive correlation with serum calcium* Hp: - sCaxP: -	uCa: no association with serum calcium/renal calcification FEPh: - hcu: 27%
Mitchell et al. 2012 n=54 eGFR calcium levels	sCa: directly associated with uCa* nHCE: - rHc: negative correlation with eGFR*	sP: not associated with eGFR Hp: - sCaxP: not associated with eGFR	uCa: directly associated with sCa* FEPh: - hcu: 26%
Ochsner Ridder et al. 2021 n=166 renal calcification renal function	sCa: no association nHCE: - rHc: -	sP: inversely with renal calcifications* Hp: - sCaxP: inversely with renal calcifications*	uCa: no association FEPh: - hcu: 66%
Saha et al. 2020 n=165 CKD stage 3 or higher (GFR < 60mL/min) nephrocalcinosis (NC)	sCa: no association nHCE: - rHc: -	sP: no association Hp: - sCaxP: direct predictor for NC*	uCa: no association FEPh: direct predictor for CKD stage 3* hcu: 20%
Underbjerg et al. 2018 n=431 any renal disease	sCa: no association nHCE: directly associated with any renal disease (OR 3.05 for 1-3 and OR 3.31 for ≥ 4 HCE)* rHc: -	sP: no association Hp: - sCaxP: directly associated with any renal disease (adjusted OR 2.21 for values above median)*	uCa: - FEPh: - hcu: -
Vadiveloo et al. 2019 (31) n=280 renal failure	mean sCa: directly associated with renal failure (eGFR<30mL/min)* nHCE: - rHc: -	sP: - Hp: - sCaxP: -	uCa: - FEPh: - hcu: -

Table 4: Overview of studies investigating biochemical parameters. author in cursive = previously analysed in systematic review by Gosmanova et al. (13),** = statistically significant (p-value<0.05), - = not investigated, OR = odds ratio.*

Biochemical control on conventional therapy has proven to be challenging (33), with only roughly one third of patients being within the biochemical range of the ESE guidelines (for serum calcium, serum phosphate, calcium-phosphate product and 24h urinary calcium). An association between conventional treatment and an increase in renal complications could be shown (26). Further research is needed to better understand, how poor biochemical control affects the kidney in hypoPT.

In conclusion, functional impairment of the kidney is observed more often in hypoparathyroid subjects than in controls, and there was a strong trend towards higher rates of renal calcification in hypoPT. Some associations with biochemical parameters like serum calcium and calcium phosphate product could be shown, however, the pathophysiology and risk factors of renal disease in hypoPT need further research.

1.5 Skeletal manifestations

PTH is an essential player in the regulation of bone remodelling. A lack or reduction of its effects on bone leads to low bone turnover and increased bone mass (see also chapter 1.1.3). Bone can be evaluated by biochemical markers of bone turnover, bone mineral density (BMD), bone biopsy/histomorphometry or markers of bone strength. Abnormalities in all the mentioned methods have been shown in patients with hypoPT, demonstrating a substantial effect on the skeleton in this disease. These complications may be reversible under PTH replacement therapy (34) (see also chapter 1.7). This chapter focuses on bone properties of patients on conventional therapy.

1.5.1 Markers of bone turnover

Markers of bone formation (like osteocalcin, procollagen type 1 amino-terminal propeptide (P1NP), or bone-specific alkaline phosphatase (BAP) and bone resorption (serum C-telopeptide, tartrate-resistant acid phosphatase 5b) can be used to assess bone turnover (7).

Bone turnover markers are typically low in hypoPT (35,36). Iglesias et al. conducted a follow-up of 25 women with postsurgical hypoPT. At baseline, BAP and osteocalcin were lower when compared to healthy individuals. All values of hypoparathyroid subjects were found to be below the normal range, but this was also the case for the control group. After a median of 10 years, final measurements were taken and all markers increased, however, the whole hypoparathyroid cohort did not differ from controls.

Another smaller study (n=14) could also show a significantly decreased level of BAP in patients with hypoPT (37).

1.5.2 Bone mineral density (BMD)

Bone mineral density (BMD) is generally elevated in patients with hypoPT compared to sex- and age-matched controls. However, it seems that there is a site-specific effect of PTH deficiency on bone. Bone density can be measured by dual energy X-ray absorptiometry (DXA, widely available) or peripheral quantitative computed tomography (pQCT, not widely available) (34). The latter also allows the analysis of bone microstructure and the differentiation between cortical and trabecular values (38).

To assess the BMD and its site-specificity in hypoPT, 11 studies were found to be relevant and analysed in this thesis. They include data on the lumbar spine, total hip, femoral neck, radius and tibia. **Table 5** gives an overview of the studies and their findings. All studies reported higher bone mineral density in hypoparathyroid patients compared to controls.

10 of them used DXA, with only one of them finding a significantly elevated BMD in all studied sites (lumbar spine, femoral neck, total hip, one third distal radius) (36). The lumbar spine showed the largest difference compared to controls in all studies and was found to have a significantly elevated BMD in 6 of the 8 studies investigating this site (36,39–43).

In contrast, measurement at the radius showed no significant difference in 2 out of 5 studies (39,40), and one even found a significantly lower BMD than in controls (44). The 3 remaining studies showed a significant increase, but one was very small (n=9 hypoPT patients) (41) and the others showed this increase only in a subgroup (36,45). The total hip BMD was also investigated in 6 studies and found to be significantly increased in 5 (36,39,40,42,43), while one showed no significant difference (44). One study had no control group therefore no comparison was possible (46).

authors, year of publication (REF), study design	country	cases	controls	methods	findings: cases vs. controls mean BMD (SD) Z score (SD) if available
Chawla et al. 2017 (39) cross-sectional study (10 year follow-up n=27)	India	104 patients with idiopathic hypoPT	64 healthy controls	**DXA:** BMD (± SD) (g/cm^2)	**lumbar spine**: 1.183 (±0.206) vs. 0.974 (±0.122)* **total hip**: 1.005 (±0.151) vs. 0.925 (± 0.121)* **ultradistal forearm**: 0.421 (±0.072) vs. 0.441 (±0.071) (other sites not shown here)
Chen et al. 2003 (41) cross-sectional study	Japan	9 women with hypoPT (6 nonsurgical, 3 postsurgical)	100 healthy adults (matched to age, gender and body size)	**DXA**: BMD (± SD) (g/cm^2) **pQCT of forearm**: Ct.vBMD, Tb.vBMD	**lumbar spine**: 1.057 (±0.148) vs. 0.793 (±0.165)* **radius**: 0.618 (±0.068) vs. 0.540 (±0.105)* *Tb.vBMD*: 157.5 (±36.7) vs. 123.4 (±47.5)* *Ct.vBMD*: 1114.1 (±53.1) vs. 1090.2 (±72.9)
				Z Score	**lumbar spine:** 1.46 (±0.59) vs -0.32 (±0.81) **radius:** 1.40 (±0.82) vs. 0.30 (±1.31)
Cipriani et al. 2021 (42) cross-sectional study	Italy	50 post women with postsurgical hypoPT	40 healthy, age-matched post women	**DXA:** aBMD (± SD) (g/cm^2)	**lumbar spine:** 1.028 (±0.160) vs. 0.945 (±0.126)* **femoral neck:** 0.952 (±1.286) vs. 0.703 (±0.1)* **total hip:** 0.921 (±0.147) vs. 0.842 (±0.104)*
Cusano et al. 2016 (45) cross-sectional study	USA	60 patients with chronic hypoPT on conventional therapy (grouped in men aged < / > 50; women <40, between 40 and 55, >55)	previously published data from CaMos (ages 20-29 and post)	**DXA**: BMD and Z Scores **HRpQCT** Tt.BMD (mg HA/cm^3)	**radius: significant differences** Z-Scores: in all women* Tt.BMD: in women <40* Ct. BMD: in women <55*, all men* **tibia: significant differences** Tt.BMD: women between 40 and 55$^+$ and >55$^+$ Ct.BMD: women <55*, women >55$^+$, men <50*
Hong et al. 2019 (43) cross-sectional study	South Korea	26 patients with hypoPT	96 age, sex and BMI-matched normal controls	**DXA**: BMD (± SD) (g/cm^2)	**lumbar spine:** 1.330 (±0.306) vs. ng* **femoral neck:** 1.060 (±0.207) vs. ng* **total hip:** 1.058 (±0.253) vs. ng*
Iglesias et al. 2019 (36) cohort study	Spain	25 women (8 pre, 17 post) with hypoPT after resection of differentiated thyroid cancer	98 euparathyroid women (14 pre, 84 post) after resection of differentiated thyroid cancer	**DXA**: BMD (± SD) (g/cm^2) after follow-up (median 10 years)	**lumbar spine**: pre: 1.17 (±0.32) vs. 1 (±0.12); post: 0.99 (±0.15) vs 0.86 (±0.12)* **femoral neck:** pre:0.97 (±0.27) vs. 0.78 (±0.11); post: 0.78 (±0.11) vs. 0.68 (±0.11)* **total hip**: pre: 1.11 (±0.22) vs. 0.95 (±0.10); post: 0.94 (±0.13) vs 0.84 (±0.13)* **1/3 distal radius** pre: 0.69 (±0.07) vs. 0.71 (±0.04); post: 0.66 (±0.05) vs. 0.59 (±0.06)*

Laway et al. 2006 (40) case-control study with intra-group comparison	India	47 patients with nonsurgical hypoPT	48 healthy volunteers (age, gender and BMI matched)	**DXA**: BMD (± SD) (g/cm^2)	**lumbar spine**: 1.098 (±0.187) vs. 0.936 (±0.0131)* **total hip**: 0.967 (±0.141) vs. 0.882 (±0.149)* **total forearm**: 0.528 (±0.079) vs. 0.536 (±0.056)
Liu et al. 2020 (38) cross-sectional study	China	94 patients with nonsurgical hypoPT	gender, age and menstrual status matched healthy individuals (pre-existing database)	**HRpQCT**: vBMD (mg HA/cm^3)	**Tt.vBMD**: r: 345.66 (±63.38) vs. 347.12 (±54.01); t: 314.15 (±51.23) vs. 303.61 (±53.63) **Ct.vBMD**: r: 932.84 (±64.67) vs. 935.15 (±48.57); t: 940.19 (±53.83) vs. 938.21 (±52.07) **Tb.vBMD**: r: 158.14 (±42.18) vs. 153.43 (±41.58); t: 170.57 (±34.32) vs. 156.48 (±40.55)*
Marcucci et al 2018 (46) retrospective observational analysis	Italy	180 patients with postsurgical and nonsurgical hypoPT	**-**	**DXA:** BMD (± SD) (g/cm^2) T Score (T) and Z Score (Z)	**lumbar spine**: 1.047 (±0.236) T: -0.2 ± 2; Z: 0.4 ± 1.9 **total femur**: 1.010 (±0.570) T: -0.3 ± 1.2; Z: 0.5 ± 1.2 **femur neck**: 0.853 (± 0.302) T: -0.8 ± 1.8; Z: 0.1 ± 1.2
Mendonca et al. 2013 (44) cross-sectional study	Brazil	16 post women with chronic postsurgical hypoPT	17 age, sex and BMI matched controls	**DXA:** BMD (± SD) (g/cm^2)	**total body**: 0.923 (±0.13) vs. 0.904 (±0.10) **proximal forearm**: 0.570 (±0.09) vs. 0.630 (±0.07)$^+$ **lumbar spine**: 1.093 (±0.26) vs. 0.970 (±0.15) **proximal femur**: 0.865 (±0.159) vs. 0.826 (±0.111) **total hip**: 0.953 (±0.162) vs. 0.961 (±0.145)
Underbjerg et al. 2018 (47) cross-sectional study	Denmark	62 patients with nonsurgical hypoPT	62 healthy age- and sex-matched controls	**DXA** : median aBMD (IQR) **HRpQCT**: vBMD mean with 95% CI (mg HA/cm^3)	**lumbar spine**: 1.129 (0.960-1.284) **femoral neck**: 0.906 (0.765-1.072) **total forearm**: 0.546 (0.499-0.594) **Tt.vBMD**: r: 307 (287-328) vs. ng; t: 303 (287-318) vs. ng **Ct.vBMD**: r: 850 (827-874) vs. ng$^+$; t: 864 (843-885) vs. ng$^+$ **Tb.vBMD**: r: 169 (158-180) vs. ng; t: 186 (175-196) vs. ng
				Z Score: (medians with IQR)	**lumbar spine**: 1.30 (0.40-2.58) vs. ng* **total hip**: 0.90 (0.00-2.10) vs. ng* **forearm**: 0.10 (-0.70-0.80) vs. ng

***Table 5**: Overview of bone mineral density. * = significantly higher, $^+$ = significantly lower, (p-value<0.05) pre = premenopausal, post = postmenopausal, ng = not given, CaMos = previously published data of the Canadian Multicenter Osteoporosis Study (CaMos), data for 20 to 29 year-olds was used (see also: https://www.camos.org/publications.php).*

Z Scores of cases and controls were given in 3 studies. One showed a significant increase in the radius of women (45) and another found significantly elevated values for lumbar spine and total hip (47). The third did not show any differences (41).

pQCT allows to assess the volumetric BMD (vBMD) of cortical and trabecular bone individually (38). This technique was used in 4 of the 11 selected studies. One only studied the cortical volumetric BMD (Ct.vBMD) in radius and tibia and found it to be significantly increased in subjects with hypoPT, when comparing them to pre-existing data from healthy 20 to 29-year-olds (45). The others investigated trabecular as well as cortical BMD. Two of them only found a significant increase in trabecular volumetric BMD (Tb.vBMD) (one in the forearm (41), the other in the tibia (38)). The latter also found an increase in Ct.vBMD in postmenopausal women and men over 50, proposing a possible age-dependent effect of hypoPT on cortical bone. Contrary to that, Ct.vBMD was even found to be significantly decreased in radius and tibia by Underbjerg and colleagues, with no change in Tb.vBMD (47).

HypoPT is a chronic disease, therefore, the long-term change of BMD is of special interest. Two studies provided data on the dynamic of skeletal metabolism in hypoPT over time.

In a 10 year follow-up of 27 patients with nonsurgical hypoPT a significant increase in BMD compared to the baseline values was found in all examined sites (lumbar spine, total hip, total forearm). The largest change was seen in the lumbar spine, followed by the forearm and the hip (39).

Another study on women with postsurgical hypoPT (n=25) and a mean follow-up of 10 years found no significant difference in BMD at baseline compared to controls, except for the lumbar spine in postmenopausal women. At the end of follow-up, postmenopausal subjects (n=22) had a significantly higher BMD than their controls at all studied sites (lumbar spine, femoral neck, total hip, one-third radius) (36). These findings are in accordance with previous results suggesting a protective effect of hypoPT on bone loss in early menopause (48).

At least in these two studies a clear dynamic of an increase in BMD over time in hypoparathyroid subjects could be shown. A significant positive correlation of disease duration with lumbar spine BMD could also be found (40,44). Furthermore, lumbar BMD was positively associated with intact PTH in serum (iPTH) (40). In the

10 year follow-up by Chawla et al. the increase in BMD at the lumbar spine was found to significantly correlate with serum phosphorus values and calcium phosphorus ratio. A significant inverse correlation of BMD of lumbar spine and forearm with serum alkaline phosphatase could be shown as well (40).

Two studies compared BMD in postsurgical and nonsurgical hypoPT. The areal BMD was found to be significantly increased in the femoral neck of nonsurgical hypoPT (1.136 ± 0.204 vs. 0.938 ± 0.152). At the other sites (lumbar spine, total hip), no significant difference was observed (43). Furthermore, total vBMD in the tibia was significantly higher in nonsurgical patients in another study (38).

In conclusion, the increase in BMD of hypoparathyroid patients is most pronounced in the lumbar spine. The data on the forearm is less conclusive, with contradictory results ranging from significant increase to significant decrease when compared to healthy controls. This supports the theory that the effect of hypoPT on bone turnover is site-specific. This may be explained by a different effect of PTH deficiency on cortical and trabecular bone, as it is already known in hyperPT (49) and for the physiological action of PTH(1) (see chapter 1.1.3). This could explain the increase in BMD of the lumbar spine, which is rich in trabecular bone - in contrast to contradictory data on the forearm, where cortical bone dominates. This is consistent with the increase in trabecular vBMD and no significant difference or even a decrease in cortical vBMD, resembling the dynamic during intermittent PTH treatment for osteoporosis (39). However, quantity alone does not guarantee a stronger and more fracture resistant bone. Bone microstructure quality needs to be considered as well and has found to be substantially altered in hypoPT (50) (see chapter 1.5.3 and 1.5.4).

1.5.3 Bone microstructure

One of the first analyses comparing iliac crest bone biopsies of hypoparathyroid patients (n=12) and age- and gender-matched controls (n=13) shows a low bone turnover with resorption and formation rates significantly decreased and significantly longer quiescent periods (51). Other studies, described in the review by Rubin et al. found trabecular bone volume to be significantly increased, either because of a higher trabecular width, number, or connectivity (52).

Cortical width was also observed to be significantly increased (53). Additionally, cortical porosity tended to be lower in hypoPT than in controls (52). To measure remodelling activity, osteoid width and surface were determined and found to be decreased in trabecular, endocortical and intracortical bone. The most pronounced reduction was seen in the trabecular envelope. In conclusion, microarchitectural abnormalities can be found in all three envelopes and are most pronounced in trabecular bone. **Figure 3** illustrates these changes in iliac crest biopsies of cases and controls. Furthermore, the mean mineralisation density was not found to be elevated in hypoPT, suggesting an augmentation in tissue volume and not in the mineralisation of bone tissue (52).

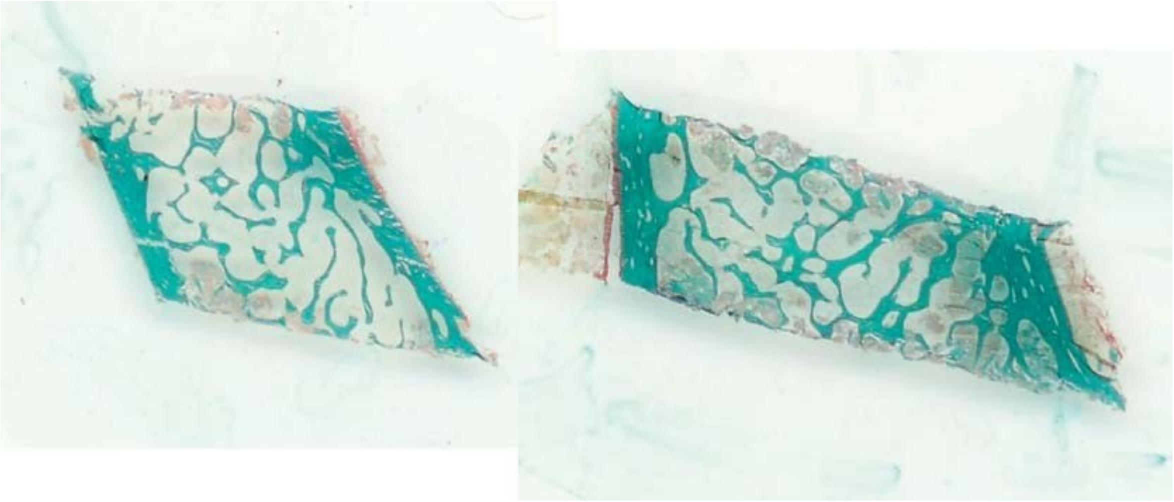


***Figure 3**: Iliac crest bone biopsies (stained with Goldner-Masson trichrome stain) from an euparathyroid (left) and hypoparathyroid (right) subject, hypoPT shows increased trabecular volume and cortical thickness* (54).

1.5.4 Bone strength and quality

Investigation of the mechanical properties of bone give additional insight into the bone quality in hypoPT.

One method that was used by several groups is the trabecular bone score (TBS). Using DXA images of the spine and evaluating the texture of gray-level images, the risk of vertebral fractures can be predicted independent of bone mineral density, with low values being a sign of a compromised microarchitecture in trabecular bone. No significant difference between the TBS of hypoparathyroid subjects compared to healthy controls could be found (n=50; 1.20 (SD 0.13) vs. 1.16 (SD 0.17), p= not significant (42) and n=26 (43)) Furthermore, there was no difference between nonsurgical and postsurgical hypoPT (43). One exception was the group of Iglesias et al. that conducted a follow-up of 25 patients with postsurgical hypoPT and compared them to women after thyroidectomy without hypoparathyroidism. At baseline TBS values did not differ significantly between cases and controls, but after 10 years of follow-up, age and gender matched controls had a significantly lower TBS than postmenopausal hypoparathyroid women. Furthermore, the prevalence of T scores < 2.5 remained stable in hypoparathyroid subjects while it increased in the control group (12% to 12% vs. 19% to 39%) (36).

Another study in 62 patients with postsurgical hypoPT found TBS to be below the normal range in over 30% of patients and in patients with fractures. Patients with low TBS were significantly older and had more comorbidities (higher BMI, glycemia and more history of fractures), suggesting that known risk factors for fractures and compromised bone quality can impair bone stability regardless of higher BMD in hypoPT, warranting a more thorough assessment of these patient concerning bone quality (55).

Another method to approximate bone strength is finite element analysis (FEA). Data of HR-pQCT scans is used to construct a model of the bone and determine ultimate stress, measured in mega pascal and failure load, measured in Newton (56,57).

It was used on 60 hypoparathyroid subjects with either postsurgical or nonsurgical hypoPT. They were split into groups by gender and age and compared to previously published data of 20 to 29 year-olds. At the radius, only women older than 55 years had a significantly decreased ultimate stress and failure load compared to the young controls (23 (SD 8) vs. 35 (SD 9) MPa and 1653 (SD 236) vs. 2993 (SD 574) N, respectively) (45).

Another method is the determination of polar strength strain index (SSIp). It was used in the radius of 9 hypoparathyroid subjects and 100 controls. No significant difference could be found (203.7 (SD 31.9) vs. 199.7 mm^3 (SD 93.7)) (41).

In a novel approach, Starr et al. determined the bone material strength index (BMSi), by using impact microindentation, to ascertain resistance to microfractures in patients with hypoPT compared to healthy controls. BMSi was found to be significantly lower by 11% in subjects with hypoPT. This contrasts with a usually higher BMD in this group, but could be explained by the low bone turnover, leading to an increased mean tissue age. In subjects with hypoPT there was a trend of decrease in BMSi with an increase in calcium supplementation, possibly indicating more severe illness. These findings may suggest an increased risk for fractures in patients with hypoPT, however it remains uncertain, whether BMSi can be used to estimate these properties correctly (58).

To conclude, there are different ways to ascertain mechanical properties of bone in hypoPT. The published studies so far have been usually small, and their results are not conclusive in comparison to healthy controls. Additionally, it is uncertain, how far they can predict fracture risk in this specific patient group, so further research in this field is needed.

1.5.5 Fracture risk

In this thesis, 10 relevant studies investigating fractures in hypoPT were identified and analysed. **Table 6** gives an overview of the studies, the fracture types and outcomes. None of them showed a significantly increased risk for fractures in general compared to healthy controls (22,30,31,36,55,59). However, fracture risk did differ significantly at specific sites.

Underbjerg and colleagues found the risk of upper extremity fractures (forearm and proximal humerus) to be significantly increased in patients with nonsurgical hypoPT. (HR 2.83; CI 95% 1.43-5.63 and HR 2.81 CI 95% 1.34-5.85, respectively) Furthermore, the risk of any upper extremity fracture was significantly higher in cases than in the population-based controls (HR 1.93 CI 95% 1.31-2.85), while there was no difference for any lower extremity fracture. Interestingly, the stratification by gender showed that only women had a significantly increased fracture risk, especially women under 18 years (n=10), when compared to controls (n=32) (30% vs. 6.3%, p=0.05, HR 18.30, CI 95% 1.89-177.56). Possible confounders that were named by the authors include seizures and cataracts, which are also more common in hypoPT and make the patients more prone to falls and consecutive fractures (30). Interestingly, the same group showed a significantly decreased risk of proximal humerus fractures in postsurgical hypoPT (59). In comparison, Kim et al. did not find a difference in humerus or wrist fractures in patients with nonsurgical hypoPT compared to controls (22).

The largest difference in fracture risk of hypoparathyroid patients could be shown at the spine. 7 studies assessed vertebral fractures (VF), with 6 of them comparing hypoparathyroid patients to controls. The following two studies focused entirely on nonsurgical hypoPT and found a significantly increased number of VFs. Chawla et al. used a cross-sectional design and found that 18.3% of patients and 4.7% of controls had VFs (OR 4.54, CI 95% 1.28-16.04), although the mean BMD at the lumbar spine was significantly increased (21.4% higher) in subjects with hypoPT. Most of the fractures (18/19) were subclinical and first detected in this study. Many cases and none of the controls had multiple VFs. A significant correlation between longer use of anticonvulsants due to seizures, which are more common in hypoPT, and VFs could be shown and may partially explain the high fracture rate. Furthermore, a significantly higher rate of VFs in postmenopausal women compared to premenopausal women was found in the hypoPT group (39). Kim et al. showed a prevalence of 4.3% VFs in hypoPT and 1.9% in controls (aHR 2.27, CI 95% 1.09-4.72) (22). These lower rates may be explained by the retrospective study design that did not allow to assess asymptomatic fractures. 3 studies on postsurgical and one study on nonsurgical hypoPT showed a nonsignificant difference in vertebral fractures (VFs in hypoPT 16% vs. 7.5% in the control group (42); 63% vs. 11.8% (44); 1.9% vs. 1.7% (59); 2.7% vs. 2.0% (30)). All identified fractures by Cipriani et al. were asymptomatic and not known before the study (42). This may be able to explain, why the rates in retrospective studies (30,59) were substantially lower compared to prospective studies where a search for VF was undertaken (42,44).

A recent meta-analysis by Pal and colleagues was able to give new insights into the somewhat inconsistent data on fracture risk in hypoPT. Using pooled analysis on data of 1470 hypoparathyroid patients, they did not find a generally increased risk for any fracture. However, VFs were more than twice as likely in patients with nonsurgical hypoPT compared to euparathyroid controls (OR 2.31, CI 95% 1.32-4.03). The other studied sites (humerus, proximal femur/hip) did not show a significant difference, also no increased risk was seen for postsurgical hypoPT. The group hypothesised that patients with nonsurgical hypoPT had a longer disease duration and the early onset of the disease may interfere with acquisition of peak bone mass. As a consequence, it seems sensible to actively screen for vertebral fractures in nonsurgical hypoPT (60). Consistent with these findings, Formenti et al. proposed a U-shaped model of the effect of PTH on vertebral fractures, with both excess and deficiency increasing the risk (see **Figure 4**).

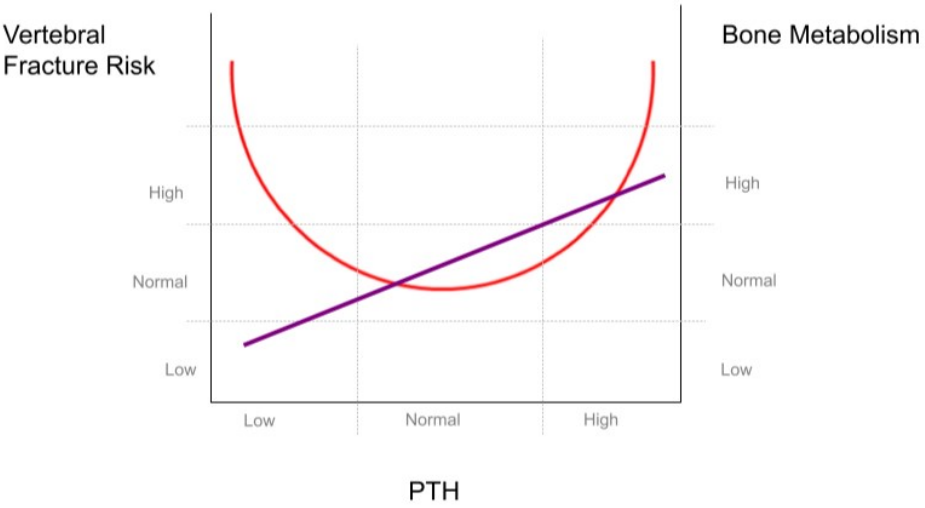


***Figure 4**: U-shaped model of fracture risk in excess and deficiency of PTH* (50)*; red: vertebral fracture risk, purple: levels of PTH.*
Reprinted by permission from Springer Nature Customer Service Centre GmbH: Springer Nature Reviews, Endocrine and Metabolic Disorders, Risk of vertebral fractures in hypoparathyroidism, Anna Maria Formenti et al (2019) (http://link.springer.com/10.1007/s11154-019-09507-x)

To conclude, bone strength depends on various properties, including mineralisation degree, hydroxyapatite and collagen properties, trabecular and cortical microarchitecture, and whole bone geometry. Every one of these factors is independently able to alter the risk for fractures (61). Normal or increased BMD is therefore not contradictory to compromised skeletal function in hypoparathyroidism, especially considering the altered microarchitecture. The increase in trabecular thickness may even impair bone strength. Its elastic properties usually help to absorb applied energy through deformation. The increase in trabecular volume may reduce this resilience, making the bone more rigid and prone to fracture (62). Furthermore, bone structure has been described as being overly mature due to a low bone turnover, again compromising its stability (58). Still, further research is needed to better understand the effect of PTH deficiency and PTH treatment on bone metabolism and structure.

author (REF), study design, country	cases (n=number)	controls (n=number)	type of fracture: case vs. control
Chawla et al. 2017 (39) cross-sectional study India	nonsurgical hypoPT (n=104)	healthy controls (n=64)	**vertebral:** 18.3% (19/104) vs. 4.7% (3/64) (OR 4.54; 1.28-16.04)*
Cipriani et al. 2021 (42)	postmenopausal women with	age matched healthy postmenopaus	**vertebral:** 16% (8/50) vs. 7.5% (3/40)

cross-sectional study Italy	postsurgical hypoPT (n=50)	al women (n=40)	
Formenti et al. 2019 (50) cross-sectional study Italy	chronic hypoPT (67 postsurgical, 4 nonsurgical)	-	**vertebral:** 18% (13/71)
Iglesias et al. 2019 (36) cohort study Spain	women with hypoPT after resection of differentiated thyroid cancer (pre=3, post=22)	euparathyroid women after resection of differentiated thyroid cancer (pre=14, post=84)	**any:** premenopausal: 0% (0/3) vs. 29% (4/14) postmenopausal: 14% (3/22) vs. 18% (21/84) (fractures occurring during 10 year follow-up)
Kim et al. 2020 (22) retrospective cohort study South Korea	nonsurgical hypoPT (n=210)	age, sex and comorbid disease matched (n=2075)	**any**: 7.1% (15/210) vs. 5.6% (116/2075) **humerus/wrist**: 3.3% (7/210) vs. 3.4% (71/2075) **vertebral**: 4.3% (9/210) vs. 1.9% (39/2075) (aHR 2.27; 1.09-4.72)* **hip**: 0% (0/210) vs. 0.5% (11/2075)
Mendonca et al. 2013 (44) cross-sectional case-control study Brazil	postmenopausal women with postsurgical hypoPT (n=16)	age, weight, hight and BMI matched (n=17)	**vertebral**: 63% (10/16) vs. 11.8% (2/17)
Sakane et al. 2019 (55) cross-sectional study Brazil	postsurgical and nonsurgical hypoPT (n=82)	-	**any:** 7.3% (6/82)
Underbjerg et al. 2014 (59) retrospective study using national health registry Denmark	postsurgical hypoPT for non-malignant cause (n=688)	matched by gender and year of birth (n=2064)	**any**: 14.8% (102/688) vs. 14.8% (305/2064) **proximal humerus**: 0.6% (4/688) vs. 2.3% (47/2064)* **vertebral**: 1.9% (13/688) vs. 1.7% (36/2064) (others not shown here)
Underbjerg et al. 2015 (30) retrospective study using national health registry Denmark	nonsurgical hypoPT (n=180)	gender- and age-matched population-based control (n=540)	**any:** 18.9% (34/180) vs. 13.0% (70/540) **vertebral:** 2.7% (5/180) vs. 2.0 (11/540) **forearm**: 8.9% (16/180) vs. 3.1% (17/540) (HR 2.83)* **proximal humerus**: 7.8% (14/180) vs. 2.6% (14/540) (HR 2.81)* **any upper extremity:** 23.3% (42/180) vs. 12.0% (65/540) (HR 1.31)* **proximal femur**: 5.0% (9/180) vs. 2.8% (15/540)
Vadiveloo et al. 2019 (31) retrospective population-based study UK	postsurgical (n=11) and nonsurgical hypoPT (n=106)	gender, age and diabetes matched from general population (n=1301)	**any**: postsurgical: 8.6% (10/116) vs. 5.5% (71/1301) nonsurgical: 8.5% (9/106)

***Table 6**: Overview of fracture risk in hypoPT; * = statistically significant (p-value<0.05), pre = premenopausal, post = postmenopausal.*

1.6 Effects of PTH replacement on the kidney

Conventional therapy is associated with adverse renal effects, with increased risk for hypercalciuria, nephrolithiasis and renal insufficiency. This is especially problematic as many patients with hypoPT already have compromised renal function before treatment (9,13,26,27,29–31,63) (see also chapter 1.4). rhPTH treatment may be a promising way to attenuate these complications, as studies have found beneficial effects of replacement therapy on kidney function and biochemical control of patients. However, it still remains uncertain, whether PTH replacement can prevent long-term complications in chronic hypoPT (33).

1.6.1 Kidney function

Kidney function, as measured by eGFR was found to be stable (64,65) or even increased (66) during once-daily rhPTH(1-84) treatment. In contrast conventional therapy is associated with a reduction in renal function (26). Chen et al. compared 69 patients on rhPTH(1-84) therapy with a historical control group not receiving PTH replacement over 5 years. However, the control group was significantly older and had a significantly higher rate of use of NSAIDs, hypocalcaemia, and diabetes mellitus type 2 at baseline. These factors may influence renal outcomes. While mean baseline eGFR was comparable between the two groups, after 5 years mean eGFR in treated patients had risen by 2.8 mL/min/1.73m^2, but declined by 8.0 mL/min/1.73m^2 in the control group. The annual decrease in eGFR differed significantly between the two groups, with a difference of 1.7 mL/min/1.73m^2 per year. **Figure 5** illustrates the results of this study (66). The stable values of eGFR were observed over 5 and 8 years in prospective studies, suggesting that rhPTH may be able to maintain eGFR over a long period of time (64,65).

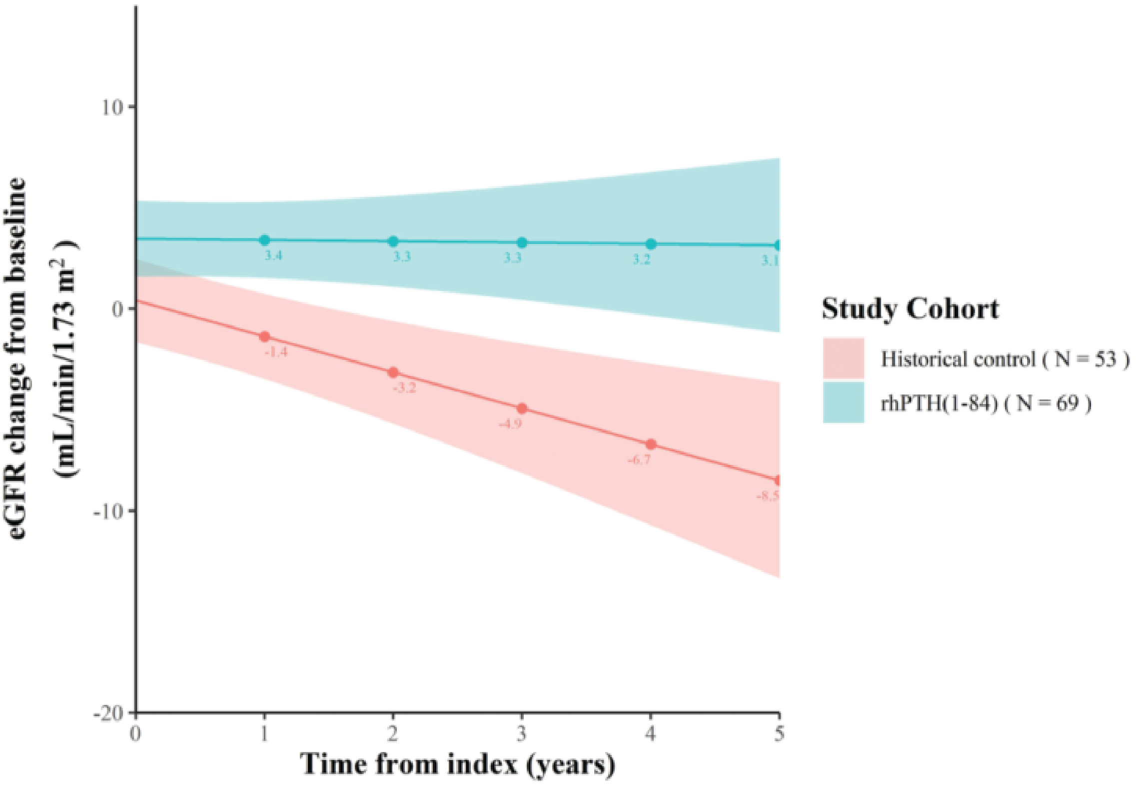


***Figure 5**: Change in eGFR in rhPTH(1-84) treatment and a historical control cohort over 5 years* (66).

1.6.2 Renal calcification

No data on renal calcification under PTH replacement therapy is available. However, considering the improved biochemical control, it may be possible that stone formation is reduced compared to conventional treatment. Research in this area could help to improve the understanding of long-term complications in hypoPT under PTH replacement.

1.6.3 Biochemical parameters

Fractional excretion of calcium was decreased by 18% after 5 years of once-daily rhPTH(1-84) replacement therapy, showing an improved effect of PTH on tubular calcium reabsorption. In consequence, mean urinary calcium excretion is decreased and then maintained within a normal range (65). This effect was observable, but not significant over 6 month (67), reaching significance after 5 (65) or even 7 years (64), suggesting that a longer treatment duration may be needed to normalise calcium excretion. In the longer study, the rate of patients with hypercalciuria also dropped from 69% to 45% (65). This difficulty in managing urinary calcium excretion was not seen in continuous subcutaneous infusion therapy of PTH(1-34) via an insulin pump. While cAMP levels, reflecting the activation of the PTH1R, rose rapidly, but only for a short time with injections, they remained elevated all day on infusion. This is mirrored in the urinary calcium excretion, as delivery by pump was able to keep it completely within the norm. This suggests that it may be necessary for the renal tubule to have constant exposure to PTH to fully activate its calcium conserving properties (68).

1.6.4 Adverse effects

One adverse effect of twice-daily hPTH(1-34) is hypocitraturia and an increase in the urinary calcium/citrate ratio (UCa/UCit), that may contribute to renal calcification and stone formation. Urinary citrate increases the solubility of calcium in the urine, preventing precipitation. Consequently, hypocitraturia is a risk factor for nephrocalcinosis and renal stones. In hPTH(1-34) therapy this effect is caused by a more pronounced decline in urinary citrate, compared to urinary calcium. Even though urinary calcium decreased in subjects, 52% showed new or progressing renal calcifications during the 5 year administration. The association with hPTH(1-34) was supported by total daily dose correlating directly with UCa/UCit and indirectly with urinary citrate. Additionally, UCa/UCit decreased after discontinuation of replacement therapy. Keeping these findings in mind, a close monitoring of kidney function and calcification is recommended (18).

Considering, that increased serum calcium concentration (27,31) and number of episodes with (relative) hypercalcaemia (11,27) are associated with adverse renal outcomes, the better biochemical control under PTH replacement may be the explanation for the improvement in kidney function when compared to conventional therapy. However, hypocitraturia may compromise renal function under replacement therapy, requiring close monitoring of patients and further research (18). Additionally, more research is needed, to determine whether replacement therapy can prevent or attenuate long-term complications (33).

1.7 Effects of PTH replacement on bone

Conventional therapy does not alter skeletal impairments in hypoPT. Replacement therapy with PTH on the other hand has a substantial positive impact on quantity and quality of bone structure (34).

1.7.1 Markers of bone turnover

In general, markers of bone turnover were found to increase rather strongly after initiation of replacement therapy, with an early peak and a consecutive decline to a steady state that is elevated compared to baseline and therefore closer to a normal bone turnover (35,65,69).

In the RACE trial, a 5-year open-label study on once-daily rhPTH(1-84) administration, the bone turnover markers cross-linked C-telopeptide of type 1 collagen (CTX), BAP and P1NP were assessed. At baseline, the means of all of them were low. They peaked after approximately one year of treatment and afterwards remained above baseline during the 5 years and within a normal range, except for P1NP that was slightly elevated. **Figure 6** shows the dynamic of CTX as an example for the changes during PTH replacement (65). Almost the same dynamic was observed in a previous study on rhPTH(1-84) administration every other day, studying s-CTX, P1NP, TRAP-5b, BAP and osteocalcin. The only difference was s-CTX, which did not show a significant increase after 24 months compared to baseline (35). In a study comparing twice daily injections to pump delivery of PTH(1-34), the continuous administration showed to be even more effective at normalising markers of bone turnover in hypoPT. While injections increased the studied markers (alkaline phosphatase, osteocalcin, NTX telopeptide, deoxypyridinoline and pyridinoline) into the upper half of or even above the normal range, the infusion managed to normalise the mean values and still increased them significantly compared to baseline (69).

In conclusion, bone turnover on PTH replacement therapy, as measured by biochemical markers, initially increases strongly and then declines into a state of more euparathyroid activity compared to baseline. This cannot be achieved by conventional therapy (34).

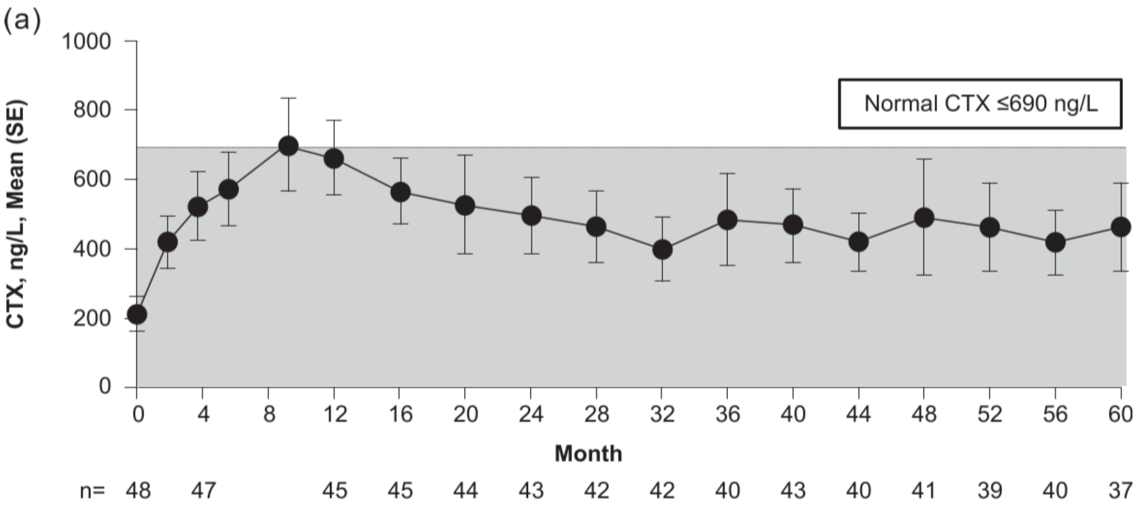


Figure 6*: Dynamic of CTX in 5 years of rhPTH(1-84) replacement* (65).

1.7.2 Bone mineral density (BMD) on PTH replacement therapy

7 studies were available to assess the change in BMD on PTH replacement therapy. **Table 7** gives an overview on the intervention, study duration and percentage change in BMD from baseline. All studies observe a significant change, however this was site and envelope specific, as was also seen under conventional therapy (see chapter 1.5.2). The lumbar spine increased the most in all studies, with changes between 2.9% (70) and 12.2% (71) and all of them being significant compared to baseline. Radius BMD was found to be significantly decreased (changes between -1.7% (72) and -3.6% (73)) in all studies investigating this site (74). Two studies used QCT. Cusano et al. found the cortical BMD to be significantly decreased in radius and tibia and a trend toward increase in trabecular BMD at the same sites (74). Sikjaer and colleagues showed a trend towards increased trabecular and decreased cortical BMD. However, only the trabecular BMD at one site (inter-trochanter region) was significant (71). These findings confirm the BMD increase in predominantly trabecular spine and the decline in predominantly cortical radius.

The site-specific effect of PTH, the increase in trabecular and the decrease in cortical bone, is already known (see also chapter 1.1.3 and 1.5.2) and can also be seen in intermittent PTH therapy for osteoporosis. In this scenario, non-vertebral and therefore dominantly cortical fractures are less likely, even though the BMD decreases. Consecutively, a decline in BMD does not necessarily mean a worse bone quality and a higher risk of fractures in hypoPT (64,72).

author, year of publication (REF) n=number of subjects country	intervention and methods	percentage change to baseline
Cipriani et al. 2017 (72) n=52 Italy	24 months of rhPTH(1-84) DXA: BMD	**lumbar spine:** +3.2%* **femoral neck**: +0.1% **total hip**: -0.18% **1/3 radius**: -1.7%*
Cipriani et al. 2018 (73) n=35 Italy	18 months of rhPTH(1-84) DXA: aBMD	**lumbar spine**: pre: +3%*; post: +3.1* **femoral neck**: pre: +0.5%; post: +1.1% **total hip**: pre: +0.7%; post: +0.7% **1/3 radius**: pre: -0.5%; post: -3.6%*
Cusano et al. 2020 (74) n=33 USA	48 months of rhPTH(1-84) DXA: BMD HR-pQCT: Ct.BMD, Tb.BMD	BMD: **lumbar spine**: +4.9%* **femoral neck**: +2.4%* **total hip**: -2.3%* **1/3 radius**: +1.0% **ultradistal radius**: -2.1%* vBMD: **radius**: Tb: +0.8%; Ct: -3.8%* **tibia**: Tb: +0.5%; Ct: -4.4%*
Rubin et al. 2010 (70) n=33 USA	24 months of rhPTH(1-84) DXA: BMD	**lumbar spine**: +2.9%* **femoral neck**: ng **distal 1/3 radius**: -2.4%*
Sikjaer et al. 2012 (71) n=17 Denmark	6 months of rhPTH(1-84) QCT: vBMD	**lumbar spine**: +12.16%* **total hip**: Tb: +1.99% Ct: -1.07% **femoral neck**: Tb: +0.70%; Ct: -3.40% **trochanter**: Tb: +0.75%; Ct: -0.14% **inter-trochanter**: Tb: +1.95%*; Ct: -2.65%
Tay et al. 2019 (64) n=24 USA	96 months of rhPTH(1-84) DXA: aBMD	**lumbar spine**: +3.8%* **femoral neck**: 0% **total hip**: +2.6%* **1/3 radius**: -3.5%*

***Table 7**: Overview of BMD in PTH replacement therapy; * = statistically significant (p-value<0.05); aBMD = areal BMD; vBMD = volumetric BMD; pre = premenopausal; post = postmenopausal; Ct = cortical; Tb = trabecular.*

1.7.3 Bone microstructure

In iliac crest bone biopsies, the largest change was seen in trabecular bone (52). After PTH treatment, trabecular thickness was found to be significantly lower, while bone surface and complexity of trabecular network increased. Furthermore, intratrabecular tunnelling, the longitudinal separation of one trabeculae into two new ones, could be observed (35,71). This phenomenon is not usually found in human bone and was significantly associated with a stronger increase in bone turnover markers. These changes were seen after a rather short time of therapy (71) and could be observed in up to 8 years of treatment (53). They represent an increase in bone turnover and a decrease in mean tissue age and therefore a more physiological state of bone metabolism and microstructure (71).

Cortical bone also showed improvement of structural abnormalities. The initially low cortical porosity increased either significantly (53,74) or showed a trend in this direction. Additionally, the number of haversian canals increased, which may be a sign of higher activity in remodelling (71). Consistent with chapter 1.7.2, cortical BMD declines as a consequence of a higher cortical porosity. However, this does not necessarily translate into a worse bone quality (74). **Figure 7** illustrates the changes in trabecular and cortical bone under PTH treatment. In conclusion, PTH replacement can improve the microstructural abnormalities and low bone turnover caused by hypoPT. However, more research is needed to assess long-time dynamics in bone with this treatment, especially the decline in cortical structures.

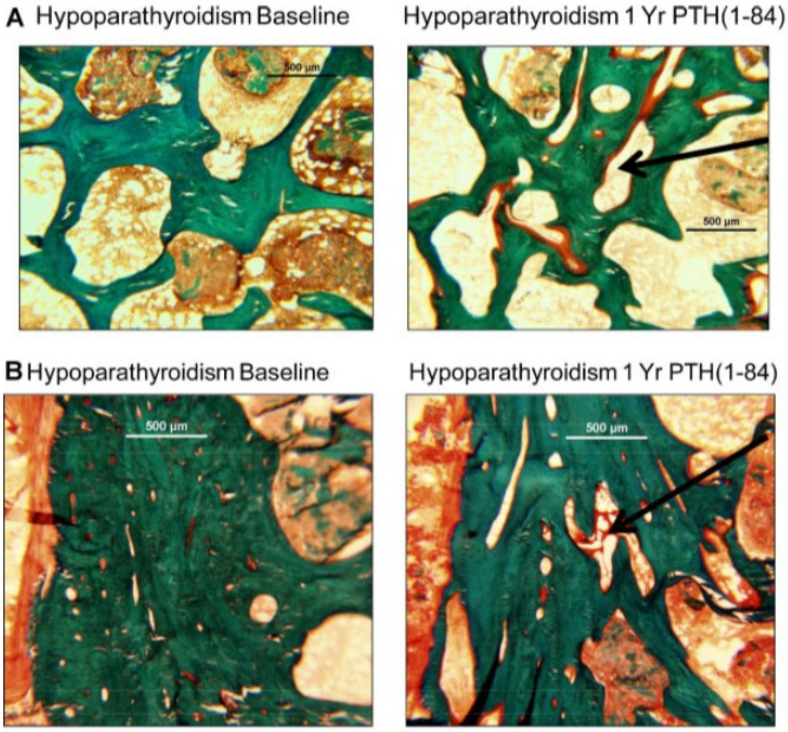


***Figure 7**: Changes in trabecular and cortical microstructure under PTH treatment, arrows show increase in trabecular tunnelling and cortical porosity after treatment* (35).

1.7.4 Bone strength

Trabecular bone score (TBS) increased significantly compared to baseline under PTH replacement therapy for 24 (72) and 18 months, with the latter study only reaching significance in premenopausal women. The authors suggest that it may take more time for the change in postmenopausal women to become significant (73).

Bone material strength index (BMSi), measured by the novel approach of microindentation, did increase significantly by 23% after a mean of 20 months of PTH administration. This shows a higher resistance to microfractures, which may be due to improved skeletal architecture. Though it must be kept in mind that the studied group only consisted of 5 subjects (58).

Rubin et al. used microfinite element analysis (µFE) and found values of bone strength, such as Force and Young's modulus, to increase significantly within the first year of PTH treatment. However, no significant difference compared to baseline could be seen at the end of the study after 2 years for any endpoint. Therefore, the authors suggest a transient improvement in skeletal properties under PTH treatment, that may also be influenced by a temporary decrease in mineralisation, resulting in a more elastic bone (75).

Cusano and colleagues found the calculated failure load to decrease significantly within 48 months of PTH replacement compared to baseline. However, the values still remained above those of normative controls. Furthermore, this decline was much smaller than expected, when considering the substantial increase in cortical porosity. Therefore, it remains unknown how much clinical endpoints, such as fracture risk, are influenced by this change (74).

In conclusion, parameters of bone strength did improve under PTH replacement, consistent with the improvement in microstructure (see chapter 1.7.3) which could not be seen under conventional treatment. However, as these are the results of rather small cohorts, further research is needed, to better understand and assess the effect of PTH on bone quality.

1.7.5 Fractures

Although PTH replacement showed beneficial effects on BMD, microstructure and bone strength, so far it is unknown how these changes affect fracture risk. A very large cohort and a long time of follow-up would be needed, to be able to assess the effect on a clinical event like fractures during PTH replacement (7,33,52).

One study is available with a duration of 8 years and found 8 fractures in 6 out of 24 patients. 10 patients reported fractures in adulthood at baseline. Notably, all fractures during the study occurred at cortical sites. However, due to the small cohort size and lack of control group, the data are not sufficient to draw a conclusion on fracture risk (64).

2 Material and Methods

This retrospective observational study was conducted as a monocentric study at the Medical University of Graz under the name “HYPOPARATHYROIDISM retrospective observational study: update 2021”. It was an update of the “Hypoparathyreoidismus Retrospektive Beobachtungsstudie” by Martin Kern in 2015.

2.1 Ethics committee and data privacy

The study was approved by the Ethics Committee of the Medical University of Graz on 05. February 2021 (EK-Nummer 33-151 ex 20/21).

The data was pseudonymised. The patients’ names were coded in an ID number, which could not be linked to the patients’ identity. The original data was only visible for authorised persons involved in this project.

2.2 Data retrieval and inclusion criteria

The retrieved data stems from patients that were treated at the Medical University of Graz/LKH Graz before July 2021. Patients were included if they had PTH levels below 30 pg/ml in combination with hypo- or normocalcaemia. There were no restrictions concerning age or sex.

Data of 226 patients were extracted from openMEDOCS by the Institute of Medical Informatics, Statistics and Documentation of the Medical University of Graz. 204 of them had a diagnosis of hypoPT, while 22 did not have a diagnosis and were viewed individually and included if they matched the inclusion criteria. The retrospective analysis was conducted by 3 medical students using the same programme by viewing each data set individually. They each used the data for their diploma thesis (Theresa Lerchl: Hypoparathyreoidismus und Fertilität, Schwangerschaft und Stillzeit, Simon Geiger: Hypoparathyroidism - a retrospective observational study: update 2021, Johanna Windisch: Hypoparathyroidism: renal and skeletal manifestations). In this process 35 patients were found to not have a chronic hypoPT or they did not have any data available and were therefore excluded from further analysis. One of those patients was initially included twice and therefore one data set was excluded. The final analysis included 191 patients.

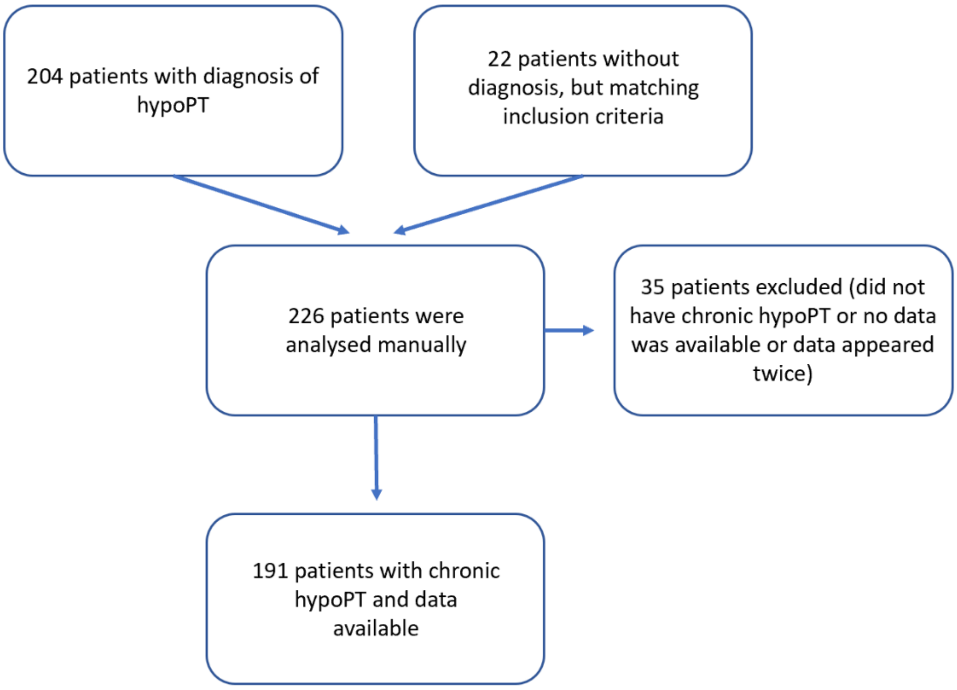


Figure 8*: Flow Chart of patient retrieval.*

The primary objective was the total serum calcium at first diagnosis. It was the main part of the diploma thesis of Simon Geiger.

In this thesis, secondary objectives regarding renal and skeletal manifestations were analysed. The following secondary objectives were assessed:

- epidemiology: age, gender, disease duration
- aetiology: postsurgical, genetic, autoimmune, idiopathic
    - for postsurgical: date, type and indication for surgery
- laboratory parameters: total serum calcium, PTH, vitamin D3, calcidiol, ionised calcium, albumin, CKMB, CK, iron parameters, eGFR, urinary calcium haemoglobin, urea, creatinine, magnesium, phosphate, PTH, transferrin, transferrin saturation, FGF23
- medication: calcium, active vitamin D, thyroid hormones, teriparatide PTH(1-34) and rhPTH1-84 (frequency, dosage)
- current symptoms of hypoPT: the most recent available entry was used, they were classified as none, mild (e.g. almost without symptoms, light fatigue, sleeping disorders, occasional light paraesthesia), medium (paraesthesia, dystonia, dyskinesia), severe (cramps, tetaniform cramps)

- co-existing diseases: renal insufficiency, dialysis, renal calcification, psychiatric disorders, epileptic seizures, fractures (number, locations and type of trauma), cataract, COVID-19, infections
- hospital stays and ICU stays
- others: birth, birth complications

Epidemiological data and the laboratory values were extracted automatically by the Institute of Medical Informatics, Statistics and Documentation of the Medical University of Graz. The remaining required information was gathered by the 3 medical students viewing the data sets.

Kidney dysfunction was defined as eGFR < 60 mL/min/1.7m^2 and the classification in accordance with the CKD criteria was used (CKD 1: eGFR ≥ 90, CKD 2: eGFR 60 – 90, CKD 3a: eGFR 45-59, CKD 3b: eGFR 30-44, CKD 4: eGFR 15-29, CKD 5: eGFR < 15). The newest available values on creatinine, eGFR and urine calcium were used. Additionally, the diagnosis of renal insufficiency was extracted manually in combination with the degree of severity based on the CKD criteria.

Because of the scarcity of different types of nonsurgical hypoPT (genetic, autoimmune, idiopathic, unknown), they were combined into one group and compared to surgical hypoPT.

2.3 Statistical analysis

IBM SPSS 27 was used for statistical analysis of the data.

Nominal and ordinal data was described with absolute and relative frequency. $p<0.05$ was defined as significant.

2.4 Limitations

Only the data available for the Medical University of Graz/LKH was analysed. Documents of examinations and treatment at other health care facilities was not included (i.e. no access to data generated at the UKH/Unfallkrankenhaus). This may underestimate the rate of certain outcomes, such as fractures and also did not allow us to investigate the exact nature of fractures. The circumstances of dialysis were not investigated further, therefore, it was not possible, to determine, whether patients had received parenteral active vitamin D during dialysis.

The patients that had died before analysis were not investigated further, therefore, no characterization regarding disease outcomes or causes of death for this group is possible. Furthermore, the patients were not contacted, therefore missing information in hospital records could not be added and the current state of the patients could not be determined. Also, without a control group, a comparison to the general population of the assessed manifestations was not possible.

3 Results

3.1 Patient characteristics

Age and gender

191 patients were included in the study. 133 (69.6%) were women and 58 (30.4%) men.

The mean age of patients still alive at the time of analysis (n=179) was 61.7 years with a standard deviation (SD) of 19.2. The youngest patient was 10 and the oldest 97 years old. Patients with nonsurgical hypoPT were significantly younger than patients with postsurgical hypoPT (48.5 ± 21.8 vs. 64.7 ± 17.3 years, $p<0.001$). The mean age of women and men did not differ significantly (62.4 ± 19.0 vs. 59.8 ± 19.8 years; $p=0.477$). 12 patients had died before analysis.

The mean duration of hypoPT for the whole group was 9.1 years (SD 5.4) with a minimum of 0 and a maximum of 29 years. Patients with postsurgical hypoPT had a non-significantly shorter duration than those with nonsurgical hypoPT (8.7 vs. 10.7 years, $p=0.105$). There was no difference between men and women (mean 9.43 years vs. 8.96 years, $p=0.777$).

Aetiology

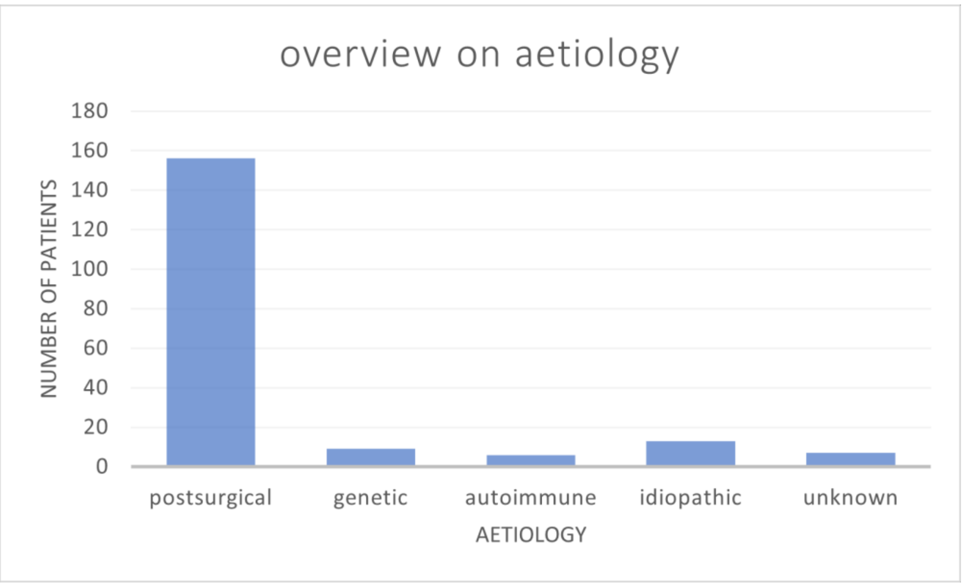


Figure 9: Histogram of aetiology: number of patients with each aetiology.

156 patients (81.7%) had postsurgical hypoPT, while 35 had nonsurgical hypoPT. 9 (4.7%), 6 (3.1%) and 13 (6.8%) had hypoPT due to genetic, autoimmune or idiopathic causes respectively. For 7 patients (3.7%) no aetiology was listed.

Postsurgical aetiology was significantly more likely in women (86.5%), than in men (70.7%) (p=0.01). Women were also two and a half times more likely to suffer from postsurgical than from nonsurgical hypoPT with an odds ratio (OR) of 2.649 (CI 95% 1.248-5.623).

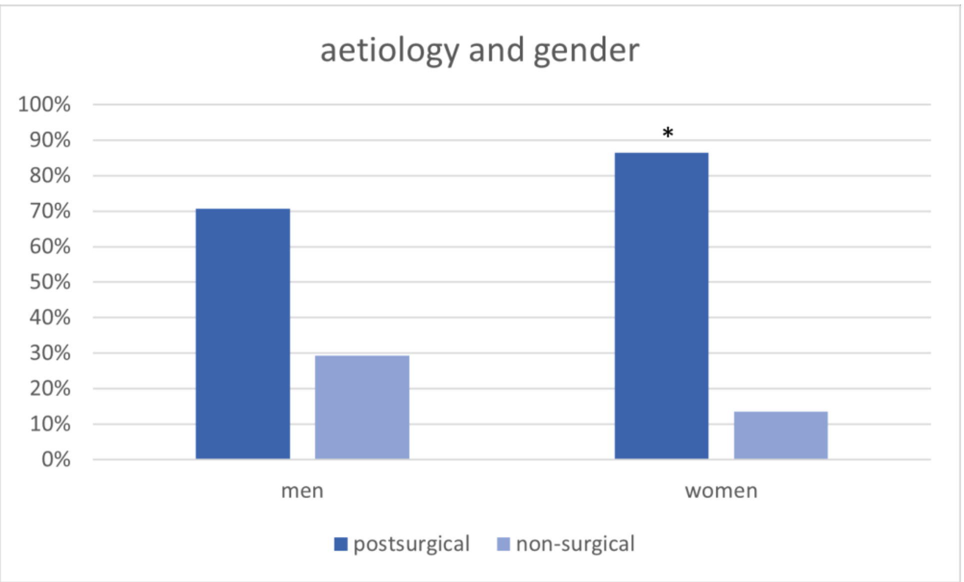


***Figure 10**: Diagram to depict differences in frequency of aetiology and gender. * = statistically significant.*

The cause for surgery in postsurgical hypoPT was

- benign thyroid disease in 48 patients (30.7%) (goiter in 34, Graves' disease in 14)
- thyroid carcinoma in 46 patients (29.5%)
- benign parathyroid disease in 13 patients (8.3%) (hyperPT in 12, parathyroid adenoma in 1)
- parathyroid carcinoma in 1 patient (0.6%)
- other causes (including MEN2A, alkali burn, oesophagus carcinoma) in 6 patients (3.8%)
- no indication was available for 42 patients (26.9%). The majority of them had had their surgery decades ago, before the implementation of the

medical information system openMEDOCS, thus, no detailed information was available.

The surgical intervention was

- total thyroidectomy (also including strumectomy) in 118 patients (75.6%)
- partial thyroidectomy (hemithyroidectomy, subtotal thyroidectomy) in 10 patients (35.3%)
- total parathyroidectomy in 8 (5.1%)
- partial parathyroidectomy 6 (3.8%)
- other interventions (including neck dissection and laryngectomy) were performed in 4 cases (2.6%)
- for 10 patients no type of intervention available (6.4%)

The causes for nonsurgical hypoPT included:

- genetic: DiGeorge-Syndrome in 4 patients, HDR syndrome in 2, and Kenny-Caffey-Syndrome in 1 patient, no further specification in 2
- autoimmune: all patients (n=6) had APS 1 (autoimmune polyendocrine syndrome 1)

The median regular calcium intake for the whole cohort was 775 mg per day (IQR 500-1200). More details for patients with different aetiologies are given in **Table 8**. The median daily calcium intake was almost twice as high in patients with postsurgical hypoPT, as compared to nonsurgical hypoPT.

aetiology	median calcium intake in mg (IQR)	median active vitamin D intake (calcitriol) in µg (IQR)
postsurgical	700 (500-1200)	0.25 (0.00-0.50)
genetic	1200 (1000-2000)	0.25 (0.00-0.50)
autoimmune	750 (600-1000)	0.50 (0.50-1.00)
idiopathic	600 (500-1000)	0.50 (0.25-1.00)
unknown	500 (500-1000)	0.00 (0.00-0.13)

Table 8: Median daily intake of calcium and active vitamin D for the different aetiologies.

3.1.1 Patients on PTH replacement therapy

11 patients in the cohort were on PTH replacement therapy at time of analysis. 10 received rhPTH(1-84) and one received rhPTH(1-34). 7 of them had postsurgical, 1

autoimmune and 3 idiopathic hypoPT. They were significantly younger than the group with standard therapy (43.6 (SD 14.2) vs. 62.9 years (SD 18.9), p=0.001) and had a shorter disease duration (4.4 vs. 9.4 years, p=0.002). There was no significance in aetiology between the two groups (36% nonsurgical vs. 17% nonsurgical, p=0.120) Renal calcification occurred in 1 patient. In this subgroup, no dialysis, kidney transplant or fracture was reported.

	PTH replacement (n=11)		conventional therapy (n=180)	
mean age in years (SD)	43.6 (14.2)		62.9 (18.9)	
gender: men I women	3	8	55	125
aetiology: postsurgical I nonsurgical (% of aetiology)	7 (64%)	4 (36%)	149 (83%)	31 (17%)
disease duration in years (SD)	**4.4 (3.9)**		**9.4 (5.4)***	
renal calcifications yes I no (%)	0 (0%)	11 (100%)	14 (8%)	166 (92%)
fractures yes I no (%)	0 (0%)	11 (100%)	29 (16%)	151 (84%)
dialysis yes I no (%)	0 (0%)	11 (100%)	13 (7%)	167 (93%)
kidney transplantation yes I no (%)	0 (0%)	11 (100%)	13 (7%)	167 (93%)

Table 9*: Overview of patients with PTH replacement therapy, compared to patients with conventional therapy, n = number of patients.*

3.2 Kidney parameters

3.2.1 eGFR

To determine the current state of eGFR, the last available measurement was used. Values were available for 163 patients. Mean eGFR was 61,3 mL/min/1.7m^2 (SD 28.2), with a minimum of 3.9 and a maximum of 123.2 mL/min/1.7m^2.

Mean eGFR of men (63.6 mL/min/1.7m^2; SD 32.0) did not differ significantly from eGFR of women (60.4 mL/min/1.7m^2; SD 26.6) (p=0.503). However, in postsurgical hypoPT the eGFR was worse compared to nonsurgical hypoPT (59.1 mL/min/1.7m^2; SD 28.1 vs. 72.8 mL/min/1.7m^2; SD 26.4, p=0.020).

CKD stage was determined using the last available eGFR measurement. Almost half of the cohort (47.3%) had renal insufficiency (CKD stage 3a or below). 26 patients had CKD 1 (16%), 60 had CKD 2 (36.8%), 32 had CKD 3a (19.6%), 19 had CKD 3b (11.7%), 14 had CKD 4 (8.6%) and 12 had CKD 5 (7.4%).

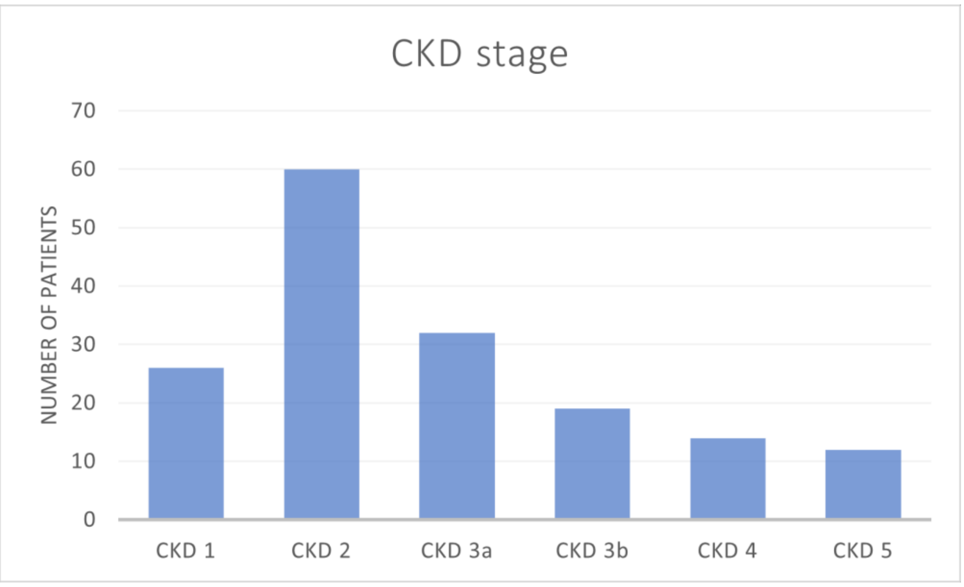


***Figure 11**: Overview of CKD stage. number of patients with CKD stage 1-5.*

The median daily calcium intake (above or below 775mg) was used to divide the patients into two groups (high vs. low). Patients with low calcium intake had a mean eGFR of 61.7 (SD 30.7), while those with high calcium intake had 60.5 (SD 26.2) (p=0.782).

3.2.2 Diagnosis of CKD

Analysing the whole group, 60 patients out of 191 had a diagnosis of CKD (31.4%) based on the KDIGO criteria.

3.2.3 Creatinine

For the estimation of current kidney function, the last available creatinine value was used. Measurements of 186 patients could be analysed. The mean value was 1.60 mg/mL (SD 1.63) and therefore above the normal range for women (1.00) and men (1.20). The minimum was 0.59 and the maximum was 12.97.

The mean creatinine of patients with postsurgical hypoPT was 1.71mg/mL (SD 1.77) and for patients with nonsurgical hypoPT 1.12mg/mL (SD 0.42). (p=0.12).

30 out of 57 men had values above the normal range (52.6%) and 61 out of 129 women (47.3%). 79 out of 152 patients (52.0%) with postsurgical hypoPT had elevated creatinine levels, compared with 12 out of 34 (35.3%) patients with nonsurgical hypoPT. There was a trend towards a higher creatinine in postsurgical hypoPT (p=0.08).

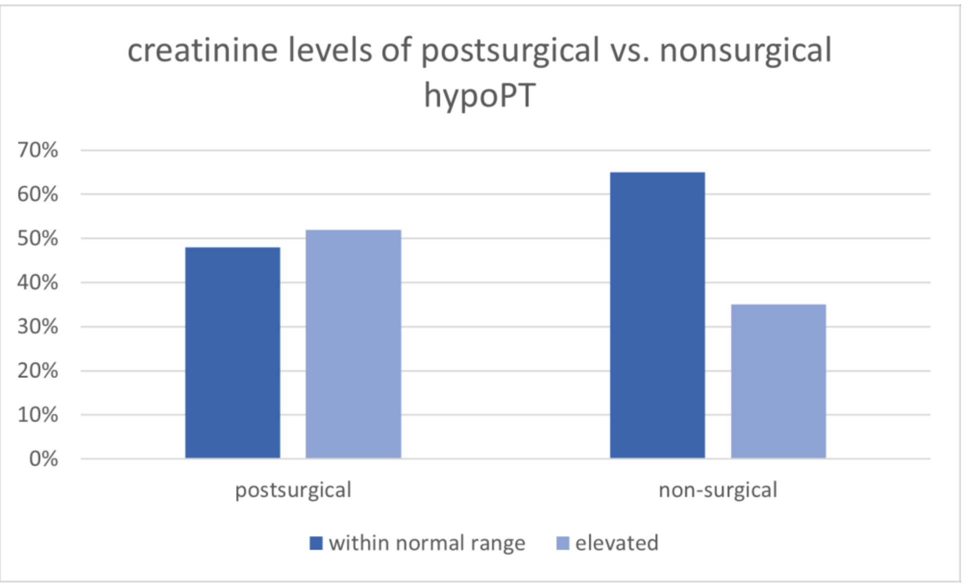


***Figure 12**: Percentage of patients within or above of normal range of creatinine.*

3.2.4 Renal calcification

For 14 patients (7.3% of the whole cohort) a history of renal calcifications (10 nephrolithiasis and 4 nephrocalcinosis) was documented. Due to the nature of the study, this prevalence is likely underestimated.

Patients with nonsurgical hypoPT had a significantly higher rate of renal calcification than those with postsurgical hypoPT (p=0.025, OR 3.83, CI 95% 1.235–11.859). 5% (n=8) of cases with postsurgical and 17% (n=6) of nonsurgical hypoPT (2 genetic, 3 idiopathic and 1 unknown aetiology) had a history of renal calcification. 22% of those with genetic hypoPT, 23% of those with idiopathic and 14% of unknown aetiology had renal calcifications. None of the patients with PTH replacement had a history of renal calcification.

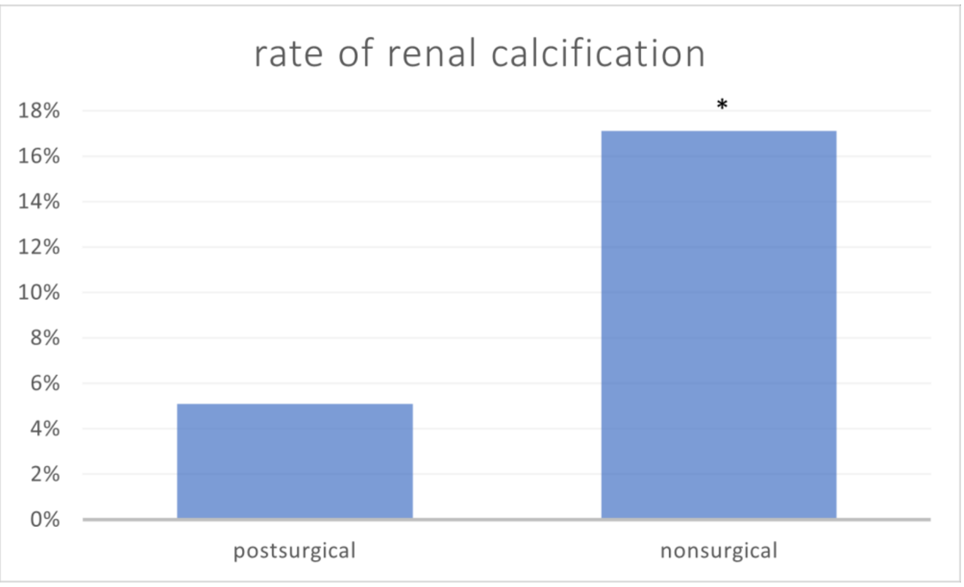


***Figure 13**: Percentage of renal calcification in postsurgical and nonsurgical hypoPT.*

Interestingly, patients with calcification were younger (mean age 57.2 years; SD 22.1) than patients without calcifications (62.0 years, SD 18.9). However, the age did not differ significantly between those groups. The youngest patient with renal calcifications was 10 years old, the oldest 97. There was no difference in disease duration between patients with and without renal calcification (11 vs. 9 years, p=0.105).

The median daily calcium intake of the group with renal calcification was 1000mg (IQR 500-1000) and therefore higher than the median of those without renal calcification (675mg, IQR 500-1200). The median daily active vitamin D (calcitriol) intake was higher as well (0.50µg IQR 0.25-0.50 vs. 0.25µg, IQR 0.00-0.50). Neither of the differences was statistically significant (p=0.97 and p=0.69, respectively).

	renal calcification (n=14)		no renal calcification (n=177)	
mean age in years (SD)	57.2 (22.1)		62.03 (10.9)	
gender: men I women	4	10	54	123
aetiology: postsurgical I nonsurgical (% of aetiology) *	**8 (5.1%)**	**6 (17.1%)**	**148 (94.9%)**	**29 (82.9%)**
median daily calcium intake in mg (IQR)	1000 (500-1000)		675 (500-1200)	
median daily active vitamin D intake in µg (IQR)	0.50 (0.25-0.50)		0.25 (0.00-0.50)	
disease duration in years (SD)	11 (5)		9 (5)	

***Table 10**: Overview of patients with renal calcification, compared to patients without renal calcification. n = number of patients.*

3.2.5 Urinary calcium

Measurements of urine calcium were available for 110 patients. The last available value was used. The mean of the whole cohort was 2.91mmol/L (SD 2.85). The minimum was 0.12 and the maximum 21.02mmol/L.

Mean urinary calcium of patients with (n=10) and without renal calcification (n=100) did not differ (2.65 (SD 2.73) vs. 2.93 mmol/L (SD 2.88), p=0.607).

There was no difference in urinary calcium values between patients with postsurgical (n=84) and nonsurgical hypoPT (n=26) (2.76 (SD 2.38) vs. 3.39mmol/L (SD 4.04), p=0.464) or patients on PTH replacement therapy (n=10) and on conventional therapy (n=100) (mean 5.39 (SD 6.24) vs. 2.66mmol/L (SD 2.18), p=0.214).

3.2.6 Dialysis and kidney transplant

There was a strong overlap between patients who had a history of dialysis and a kidney transplant. 7 patients had a history of dialysis and a kidney transplant and 6 each had either only dialysis or kidney transplant. In total, 13 patients (6.8%) had a history of dialysis and 13 patients (6.8%) had received a kidney transplant. No dialysis or kidney transplantation was documented for patients with PTH replacement therapy.

13 patients (6.8%) had a history of dialysis. All of them had postsurgical hypoPT. Their mean age was 63.3 years (SD 18.9). Disease duration did not differ between patients with and without dialysis. The median daily oral active vitamin D intake was significantly lower, than in the group without dialysis, mainly because the majority did not take any oral vitamin D (0.00µg, IQR 0.00-0.00 vs. 0.50µg, IQR 0.00-0.50, p=0.001). The median calcium intake did not differ between patients needing dialysis and the others (1000mg, IQR 0-2500 vs. 750mg, IQR 500-1200; p=1.000).

There was no indication for dialysis given available. However, it is very likely, that those that received a kidney transplant later on had dialysis for the same reason as the transplantation. 5 patients had hypertension, diabetes mellitus type 2 or both, the leading causes for dialysis in general.

	dialysis (n=13)		no dialysis (n=178)	
mean age in years (SD)	63.3 (18.9)		61.6 (19.3)	
gender: men I women	6	7	52	126
aetiology: postsurgical I nonsurgical (% of aetiology)	13 (8.3%)	0 (0.0%)	143 (91.7%)	35 (100%)
median daily calcium intake in mg (IQR)	1000 (0-2500)		750 (500-1200)	
median daily active vitamin D intake in µg (IQR)*	**0.00 (0.00-0.00)**		**0.50 (0.00-0.50)**	
Disease duration in years (SD)	9 (5)		9 (5)	
number and rate of renal calcifications	1 (7.7%)		13 (7.3%)	

***Table 11**: Comparison of patients with and without dialysis regarding age, gender, aetiology and medication. n = number of patients.*

13 patients had a kidney transplant. They all had postsurgical hypoPT and their mean age was 61.4 years. The youngest patient was 33 years old. Reasons for transplantation were given in 7 patients (systemic lupus erythematosus, chronic glomerulonephritis in two patients, cystic kidney, membranoproliferative glomerulonephritis, familial nephropathy and atrophic kidney).

	kidney transplant (n=13)		no kidney transplant (n=178)	
mean age in years (SD)	61.4 (17.5)		61.7 (19.4)	
gender: male I female	6	7	52	126
aetiology: postsurgical I nonsurgical (% of aetiology)	13 (8.3%)	0 (0.0%)	143 (91.7%)	35 (100%)
median daily calcium intake in mg (IQR)	600 (0-1000)		800 (500-1200)	
median daily active vitamin D intake in µg (IQR)	0.00 (0.00-0.25)		0.50 (0.00-0.50)	
Disease duration in years (SD)	9.1 (5.1)		9.1 (5.5)	
number and rate of renal calcifications	0 (0%)		14 (8%)	

***Table 12**: Comparison of patients with and without kidney transplant regarding age, gender, aetiology and medication. n = number of patients.*

3.3 Bone parameters

3.3.1 Number of fractures

In total, 53 fractures were documented for the whole cohort (14 patients had one, 15 had up to 4 fractures). 32 fractures occurred in patients with postsurgical and 21 in patients with nonsurgical hypoPT.

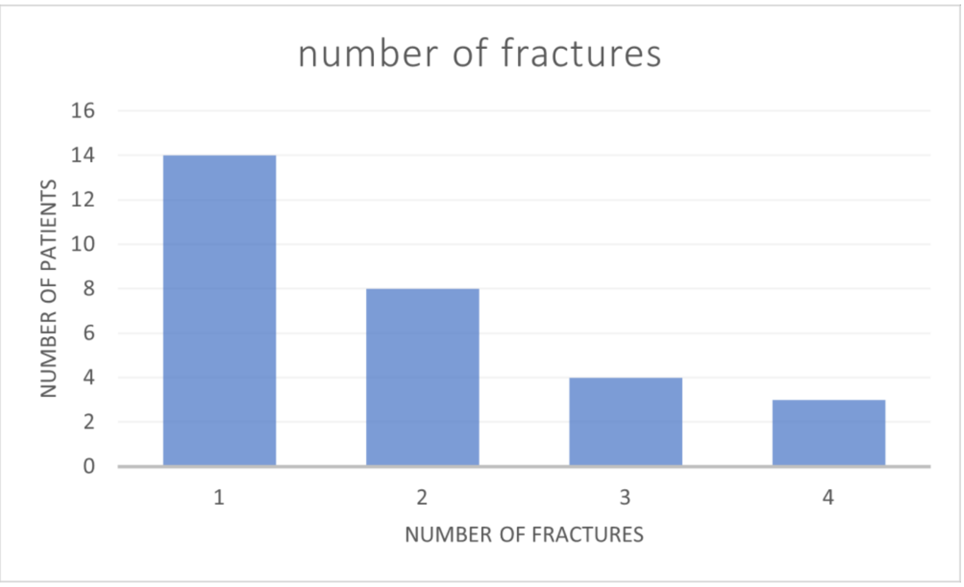


***Figure 14**: Number of fractures per patients. 162 had no fractures.*

29 patients (15.2%) had a history of at least one fracture. 19 had postsurgical hypoPT and 10 nonsurgical hypoPT. The fractures in nonsurgical hypoPT occurred in 1 patient with genetic, 2 with autoimmune, 5 with idiopathic and 2 with unknown aetiology. Patients with nonsurgical hypoPT had a significantly higher fracture risk, when compared to postsurgical hypoPT (29% vs. 12%; p=0.033; OR 2.884, CI 95% 1.201 - 6.928). No fractures were documented for patients on PTH replacement therapy.

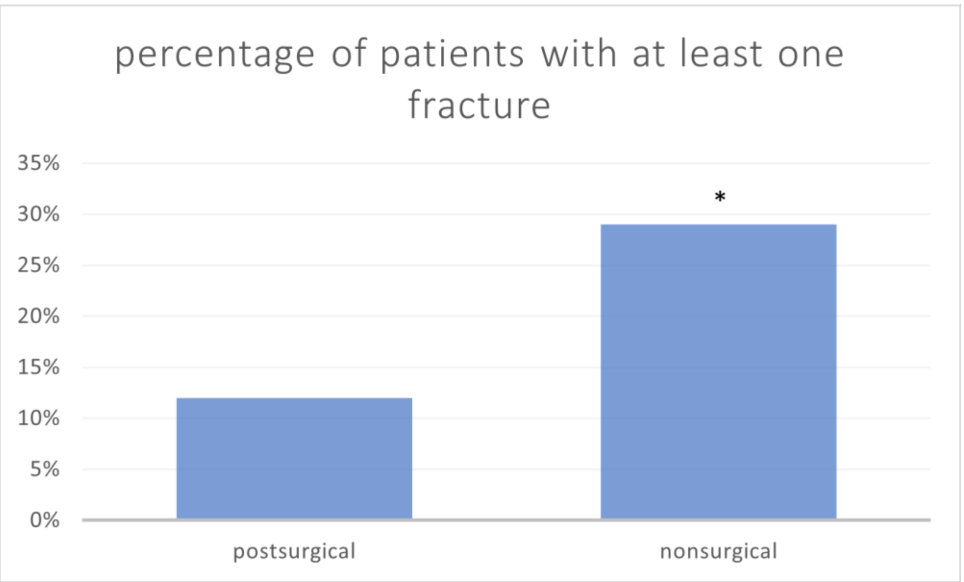


***Figure 15**: Percentage of patients with at least one fracture.*

3.3.2 Location of fracture

Proximal femur fractures and other lower extremity fractures (tibia, fibula, patella, non-proximal femur, ankle, calcaneus, hip) occurred significantly more often in nonsurgical hypoPT than in postsurgical hypoPT (11.4% vs. 0.6%, p=0.004 and 17.1% vs. 3.2%, p=0.006, respectively). All other types of fractures were more common in nonsurgical hypoPT as well, however the differences did not reach significance. **Table 13** gives an overview on frequency of types of fractures in nonsurgical and postsurgical hypoPT.

type of fracture	nonsurgical (n=35)	postsurgical (n=156)	p value (OR, CI 95%)
any	10 (28.6%)	19 (12.2%)	**0.033 (2.88; 1.20-6.93)***
vertebral	3 (8.6%)	7 (4.5%)	0.394 (2.00; 0.49-8.14)
proximal femur	4 (11.4%)	1 (0.6%)	**0.004 (20.00; 2.16-185.07)***
radius	1 (2.9%)	2 (1.3%)	0.46 (2.27; 0.20-25.70)
other lower extremity	6 (17.1%)	5 (3.2%)	**0.006 (6.25; 1.79-21.84)***
other upper extremity	1 (2.9%)	2 (1.3%)	0.457 (2.27; 0.20-25.70)
face	2 (5.7%)	2 (1.3%)	0.154 (4.67; 0.63-34.33)
thorax	1 (2.9%)	3 (1.9%)	0,558 (1.50; 0.15-14.86)

***Table 13**: Overview of fracture type and aetiology (patients with at least one fracture in the location and % of aetiology): other lower extremity (tibia, fibula, patella, non-proximal femur, ankle, calcaneus, hip), other upper extremity (metacarpal, scaphoid), face (nose, orbita, skull), thorax (ribs, clavicula).*

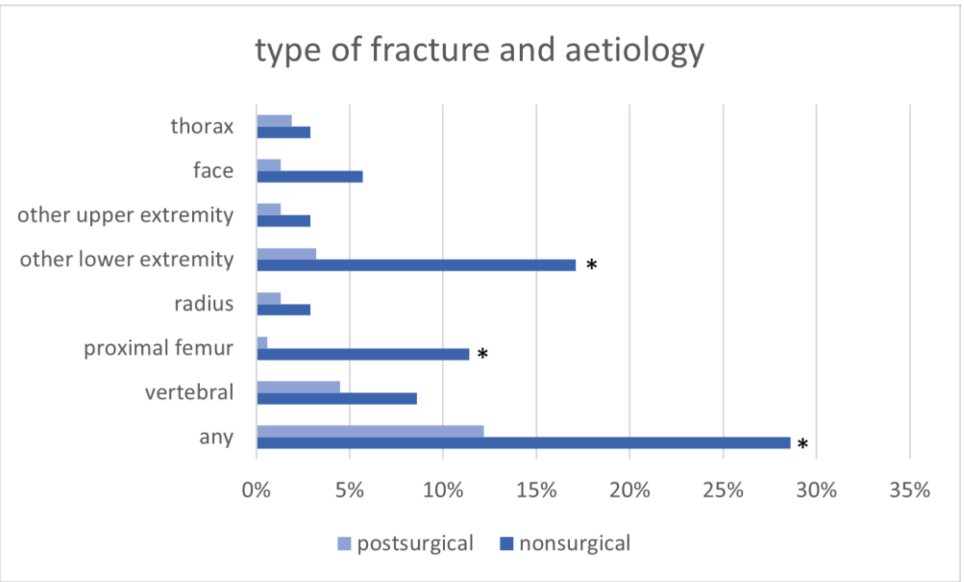


***Figure 16**: Type of fracture for postsurgical and nonsurgical hypoPT. * = statistically significant; other lower extremity (tibia, fibula, patella, non-proximal femur, ankle, calcaneus, hip), other upper extremity (metacarpal, scaphoid), face (nose, orbita, skull), thorax (ribs, clavicula).*

3.3.3 Type of fracture

Most fractures occurred because of osteoporosis (n=21), followed by inadequate trauma (including fall and stress fractures) (n=16) and unknown trauma (n=12). Only 4 fractures happened after an adequate trauma (e.g. car accident). In the group with nonsurgical hypoPT more fractures with inadequate trauma happened (57.1% vs. 12.5%). However, it needs to be noted, that one nonsurgical patient had 4 fractures due to inadequate trauma.

trauma	total (n=53)	postsurgical (n=32)	nonsurgical (n=21)
adequate	4 (7.5%)	4 (12.5%)	0 (0.0%)
osteoporotic	21 (39.6%)	14 (43.8%)	7 (33.3%)
inadequate	16 (30.2%)	4 (12.5%)	12 (57.1%)
unknown	12 (22.6%)	10 (31.2%)	2 (9.5%)

***Table 14**: Overview of trauma that caused a fracture for postsurgical and nonsurgical hypoPT.*

3.3.4 BMD

T-Scores of lumbar spine were available for 45 patients (mean 0.75, SD: 2.38) and of proximal femur for 37 patients (mean 0.13, SD: 1.76). Notably, T Scores of lumbar spine had a higher variability (SD: 2.38) than those of proximal femur (SD 1.76). Z Scores of 28 patients for lumbar spine (mean: 0.86, SD: 2.08) and of 22 patients for proximal femur (mean: 0.78, SD: 1.53) could be analysed. For values on other locations, details are given in **Table 15**. There was a remarkable variability of T and Z scores in lumbar spine (T Score: minimum -3.6, maximum 7.8 and Z Score. minimum -5.4, maximum 5.2)

location and value	mean (SD)	maximum	minimum
lumbar spine: T Score (n=45)	0.75 (2.38)	7.8	-3.6
lumbar spine Z Score (n=28)	0.86 (2.08)	5.2	-5.4
lumbar spine TBS (n=10)	1.40 (0.12)	1.538	1.182
proximal femur: T Score (n=37)	0.13 (1.76)	4.8	-2.6
proximal femur: Z Score (n=22)	0.78 (1.53)	3.9	-2.5
non-proximal femur: T Score (n=6)	0.33 (1.17)	2.3	-1.1
non-proximal femur: Z Score (n=4)	0.30 (0.76)	1.4	-0.3
hip: T Score (n=12)	0.38 (2.05)	4.1	-2.4
hip: Z Score (n=7)	0.66 (1.52)	3.3	-1.3

radius: T Score (n=5)	-1.06 (2.31)	1.2	-4.5
radius: Z Score (n=3)	0.70 (0.35)	0.9	0.3

Table 15*: T and Z Scores for lumbar spine, proximal femur, non-proximal femur, hip and radius. n = number of values available.*

To compare bone density between aetiologies, T and Z Scores were calculated for postsurgical and nonsurgical hypoPT individually, there were no significant differences between groups. T Score of lumbar spine had a mean of 0.9 and 0.2, respectively and Z Score a mean of 0.9 and 0.7 respectively (p=0.262 and p=0.380). The mean of proximal femur T Score was 0.1 and 0.2, respectively. The mean of Z Score was 0.9 and 0.3 respectively (p=0.865 and p=0.538).

4 Discussion

This is the largest Austrian observational study to date, using retrospective data from the hospital information system of the Medical University of Graz.

The aim of this part was to describe the effect of hypoPT on renal and skeletal outcomes and to assess whether there are differences between postsurgical and nonsurgical patients. Additionally, the current literature was summarized and compared to the results of this study.

The composition of the cohort was very similar to published observational studies. The majority of patients in this study were women (69.9%), similar to other studies investigating both postsurgical and nonsurgical hypoPT (69.3% (31), 76.2% (20) and 79.5% (12)). This was even more evident for the postsurgical group (115 women). This can be explained by the high rate of postsurgical hypoPT after thyroid surgery, which is more often performed in women.

Disease duration did not differ between postsurgical and nonsurgical hypoPT (mean 8.7 vs. 10.7 years, $p=0.105$), however the date of diagnosis may not always coincide with date of onset. Particularly in nonsurgical hypoPT, long delays have been described.

Daily rhPTH 1-84 therapy is available in Austria since 2018. Overall, 11 patients received replacement therapy in our cohort (10 received rhPTH(1-84) and one received rhPTH(1-34)).

Renal outcomes

In our cohort, patients with postsurgical hypoPT had a significantly lower eGFR than patients with nonsurgical hypoPT (59.1 vs. 72.8 mL/min/1.7m^2, $p=0.02$). This may primarily be explained by the fact that the patients with postsurgical hypoPT were significantly older than those with nonsurgical hypoPT (64.7 vs 48.5 years, $p<0.001$), as kidney function declines with age.

The mean eGFR of the whole cohort (61.3mL/min/1.7m^2) is equal to a CKD stage 2, which means that at least mild impairment of renal function can be found in most individuals of the cohort. The mean creatinine level (1.60mg/mL) was above the normal range (1.0mg/mL for women and 1.2mg/mL for men), further confirming the high rate of renal dysfunction in the cohort.

47% of the cohort had CKD stage 3a or lower, but only 31% had a diagnosis of CKD. As only the last eGFR value was analysed an AKI could not be differentiated from CKD in this study. Nevertheless, both rates are high compared to the range found by the recent review by Gosmanova et al. ranging from 2.5% to 41% (13) and also the findings on control groups ranging from 0.7% (9) to 1.5% (30).

7.3% of our cohort had documented renal calcification (nephrolithiasis and/or nephrocalcinosis). In studies including postsurgical and nonsurgical hypoPT, such as those by Gafni et al. (18) or Ochsner Ridder et al. (12), the rates were higher with 42.6% and 48.4%, respectively. This can be explained by study design (prospective and retrospective cohorts with renal imaging for all subjects or only when indicated). The retrospective study design of our investigation does not allow to exclude asymptomatic renal calcification, so the real rate of renal calcifications in our cohort may be substantially higher, too.

Remarkably, patients with nonsurgical hypoPT were almost 4 times more likely to have renal calcification than those with postsurgical hypoPT (17.1% vs. 5.1%, p=0.025, OR 3.83, CI 95% 1.235-11.859). The rate of renal calcification in nonsurgical hypoPT in the literature is reported to range from 1.1% (30) to 11% (28).

Dialysis and kidney transplants only occurred in patients with postsurgical hypoPT. None of them were directly linked to complications of hypoPT or adverse effects of its treatment. A possible explanation would be the significant difference in age, resulting in more comorbidities in this group, leading to renal injury.

Skeletal outcomes

29 patients (13.6%) in the cohort had a history of at least one fracture and 53 fractures were documented for the entire cohort. (which occurred in 15.2% of the total cohort). Patients with nonsurgical hypoPT had a significantly higher fracture risk compared to postsurgical patients, despite much younger age (28.6% vs. 12.2%, p=0.033). Fractures occurred more often in nonsurgical hypoPT. Particularly, the rate of proximal femur and other lower extremity fractures was

significantly higher in nonsurgical patients. It has been hypothesized that the lack of PTH in early life, as it may happen in nonsurgical hypoPT, interferes with the acquisition of peak bone mass and therefore diminishes bone quality more than a late onset of hypoPT (60). Additionally, patients with nonsurgical hypoPT usually have a longer disease duration which may explain the higher rate of complications.

The rate of diagnosed vertebral fractures was 8.6% for nonsurgical and 4.5% for postsurgical patients. In comparison to the meta-analysis on fracture risk by Pal et al. (60) the rate of any fracture in the whole cohort was comparable (7.1% to 18.9%), while the rate in nonsurgical cases alone was above that. The described rate of vertebral fractures in our study was lower than in the meta-analysis (1.9% to 62.5%). However, it is well known that vertebral fractures often go undiagnosed, and therefore the actual number of fractures is likely underestimated in our analysis.

Additionally, fractures reported and/or treated in other hospitals were not available for analysis.

Many fractures were reported to be caused by osteoporosis (39.6%) and may therefore only in part be attributed to the skeletal changes in hypoPT. Low trauma fractures may primarily be explained by the changes in microarchitecture without a loss of BMD, as has been suggested before (61).

The mean TBS Score (where available) was 1.40 and can therefore considered to be normal (normal microarchitecture above 1.350).

It would be very interesting to compare the findings of this study to a matched control group. This way the risk of renal and skeletal manifestations in hypoPT could be assessed more reliably in comparison to the general population.

Conclusions

Our cohort represents one of the largest observational cohorts on hypoPT. We were able to confirm the demographics of other cohorts and the high renal and skeletal morbidity in both postsurgical and nonsurgical hypoPT patients. Interestingly, despite younger age, fractures and renal calcifications were significantly more frequent in nonsurgical patients, while worse renal function was seen in the postsurgical group.

There are a number of limitations, contributable mostly to the retrospective observational character of our study, where underreporting of many endpoints is most likely. Additionally, we are unable to compare the findings of our study to a matched control group. Also, it is impossible to perform a meaningful analysis for differences between conventional and rhPTH 1-84 therapy because of the small number of individuals and the short treatment interval of 3 years or less.

Further studies are certainly necessary to answer many questions for this special patient group and to identify modifiable risk factors that could mitigate the high risk for adverse renal and skeletal outcomes.

Literature

1. Goltzman D. Physiology of Parathyroid Hormone. Endocrinol Metab Clin North Am. 2018;47(4):743–58.
2. Horn F. Biochemie des Menschen. 8th ed. Stuttgart; 2020. 485–498 p.
3. Wang X, Cheng X, Zhao L, Wang Y, Ye C, Zou X, et al. Molecular insights into differentiated ligand recognition of the human parathyroid hormone receptor 2. Proc Natl Acad Sci. 2021 Aug 10;118(32):e2101279118.
4. Larsson S, Jones HA, Göransson O, Degerman E, Holm C. Parathyroid hormone induces adipocyte lipolysis via PKA-mediated phosphorylation of hormone-sensitive lipase. Cell Signal. 2016 Mar;28(3):204–13.
5. Van Abel M, Hoenderop JGJ, Van Der Kemp AWCM, Friedlaender MM, Van Leeuwen JPTM, Bindels RJM. Coordinated control of renal Ca2+ transport proteins by parathyroid hormone. Kidney Int. 2005;68(4):1708–21.
6. Silva BC, Bilezikian JP. Parathyroid hormone: anabolic and catabolic actions on the skeleton. Curr Opin Pharmacol. 2015;22(6):41–50.
7. Bilezikian JP. Hypoparathyroidism. J Clin Endocrinol Metab. 2020;105(6):1722–36.
8. Bollerslev J, Rejnmark L, Zahn A, Heck A, Appelman-Dijkstra NM, Cardoso L, et al. European expert consensus on practical management of specific aspects of parathyroid disorders in adults and in pregnancy: recommendations of the ESE Educational Program of Parathyroid Disorders (PARAT 2021). Eur J Endocrinol. 2022 Feb 1;186(2):R33–63.
9. Bergenfelz A, Nordenström E, Almquist M. Morbidity in patients with permanent hypoparathyroidism after total thyroidectomy. Surg (United States). 2019;167(1):124–8.
10. Cusano NE, Bilezikian JP. Signs and Symptoms of Hypoparathyroidism. Endocrinol Metab Clin North Am. 2018;47(4):759–70.
11. Underbjerg L, Sikjaer T, Rejnmark L. Long-Term Complications in Patients With Hypoparathyroidism Evaluated by Biochemical Findings : A Case-

Control Study. J Bone Miner Res. 2018;33(5):822–31.

12. Ochsner Ridder L, Harsløf T, Sikjær T, Underbjerg L, Rejnmark L. Determinants of hypercalciuria and renal calcifications in chronic hypoparathyroidism : A cross- - sectional study. Clin Endocrinol (Oxf). 2021;(March):1–9.

13. Gosmanova EO, Houillier P, Rejnmark L, Marelli C, Bilezikian JP. Renal complications in patients with chronic hypoparathyroidism on conventional therapy: a systematic literature review: Renal disease in chronic hypoparathyroidism. Rev Endocr Metab Disord. 2021;

14. Gafni RI, Collins MT. Hypoparathyroidism. Solomon CG, editor. N Engl J Med. 2019 May 2;380(18):1738–47.

15. Arlt W, Fremerey C, Callies F, Reincke M, Schneider P, Timmermann W, et al. Well-being, mood and calcium homeostasis in patients with hypoparathyroidism receiving standard treatment with calcium and vitamin D. Eur J Endocrinol. 2002;146(2):215–22.

16. Astor MC, Løvås K, Debowska A, Eriksen EF, Evang JA, Fossum C, et al. Epidemiology and Health-Related Quality of Life in Hypoparathyroidism in Norway. J Clin Endocrinol Metab. 2016 Aug;101(8):3045–53.

17. David K, Moyson C, Vanderschueren D, Decallonne B. Long-term complications in patients with chronic hypoparathyroidism: a cross-sectional study. Eur J Endocrinol. 2019 Jan;180(1):71–8.

18. Gafni RI, Langman CB, Guthrie LC, Brillante BA, James R, Yovetich NA, et al. Hypocitraturia Is an Untoward Side Effect of Synthetic Human Parathyroid Hormone (hPTH) 1-34 Therapy in Hypoparathyroidism That May Increase Renal Morbidity. J Bone Miner Res. 2018;33(10):1741–7.

19. Hadker N, Egan J, Sanders J, Lagast H, Clarke BL. Understanding the Burden of Illness Associated with Hypoparathyroidism Reported Among Patients in the Paradox Study. Endocr Pract. 2014 Jul;20(7):671–9.

20. Ketteler M, Chen K, Gosmanova EO, Signorovitch J, Mu F, Young JA, et al. Risk of Nephrolithiasis and Nephrocalcinosis in Patients with Chronic

Hypoparathyroidism: A Retrospective Cohort Study. Adv Ther. 2021;38(4):1946–57.

21. Kim JH, Shin Y-L, Yang S, Cheon CK, Cho JH, Lee BH, et al. Diverse genetic aetiologies and clinical outcomes of paediatric hypoparathyroidism. Clin Endocrinol (Oxf). 2015 Dec;83(6):790–6.
22. Kim SH, Rhee Y, Kim YM, Won YJ, Noh J, Moon H, et al. Prevalence and complications of nonsurgical hypoparathyroidism in Korea: A nationwide cohort study. PLoS One. 2020;15(5).
23. Leidig-Bruckner G, Bruckner T, Raue F, Frank-Raue K. Long-Term Follow-Up and Treatment of Postoperative Permanent Hypoparathyroidism in Patients with Medullary Thyroid Carcinoma: Differences in Complete and Partial Disease. Horm Metab Res. 2016 Nov 3;48(12):806–13.
24. Levy I, Licht C, Daneman A, Sochett E, Harrington J. The Impact of Hypoparathyroidism Treatment on the Kidney in Children: Long-Term Retrospective Follow-Up Study. J Clin Endocrinol Metab. 2015 Nov;100(11):4106–13.
25. Lopes MP, Kliemann BS, Bini IB, Kulchetscki R, Borsani V, Savi L, et al. Hypoparathyroidism and pseudohypoparathyroidism: etiology, laboratory features and complications. Arch Endocrinol Metab. 2016 Dec;60(6):532–6.
26. Meola A, Vignali E, Matrone A, Cetani F, Marcocci C. Efficacy and safety of long-term management of patients with chronic post-surgical hypoparathyroidism. J Endocrinol Invest. 2018;41(10):1221–6.
27. Mitchell DM, Regan S, Cooley MR, Lauter KB, Vrla MC, Becker CB, et al. Long-term follow-up of patients with hypoparathyroidism. J Clin Endocrinol Metab. 2012;97(12):4507–14.
28. Saha S, Kandasamy D, Sharma R, Bal C, Sreenivas V, Goswami R. Nephrocalcinosis, Renal Dysfunction, and Calculi in Patients With Primary Hypoparathyroidism on Long-Term Conventional Therapy. J Clin Endocrinol Metab. 2020;105(4):1215–24.
29. Underbjerg L, Sikjaer T, Mosekilde L, Rejnmark L. Cardiovascular and Renal

Complications to Postsurgical Hypoparathyroidism : A Danish Nationwide Controlled Historic Follow - Up Study. J Bone Miner Res. 2013;28(11):2277–85.

30. Underbjerg L, Sikjaer T, Mosekilde L, Rejnmark L. The epidemiology of nonsurgical hypoparathyroidism in Denmark: A nationwide case finding study. J Bone Miner Res. 2015;30(9):1738–44.

31. Vadiveloo T, Donnan PT, Leese CJ, Abraham KJ, Leese GP. Increased mortality and morbidity in patients with chronic hypoparathyroidism: A population-based study. Clin Endocrinol (Oxf). 2019;90(2):285–92.

32. Bollerslev J, Rejnmark L, Marcocci C, Shoback DM, Sitges-serra A, Biesen W Van, et al. European Society of Endocrinology Clinical Guideline : Treatment of chronic hypoparathyroidism in adults. Eur J Endocrinol. 2015;173(2).

33. Zavatta G, Clarke BL. Challenges in the management of chronic hypoparathyroidism. Endocr Connect. 2020;9(10):229–40.

34. Rubin MR. Skeletal Manifestations of Hypoparathyroidism. Endocrinol Metab Clin North Am. 2018;47(4):825–37.

35. Rubin MR, Dempster DW, Sliney J, Zhou H, Nickolas TL, Stein EM, et al. PTH(1-84) Administration Reverses Abnormal Bone-Remodeling Dynamics and Structure in Hypoparathyroidism. J Bone Miner Res. 2011;26(11):2727–36.

36. Iglesias SG, Dominguez MLDM, Herrero EF, Martinez-Pueyo JI, Arroba CMA, Diaz-Guerra GM, et al. Trabecular bone score and bone mineral density in patients with postsurgical hypoparathyroidism after total thyroidectomy for differentiated thyroid carcinoma. Surgery. 2019;165(4):814–9.

37. Chan FKW, Tiu SC, Choi KL, Choi CH, Kong APS, Shek CC. Increased bone mineral density in patients with chronic hypoparathyroidism. J Clin Endocrinol Metab. 2003;88(7):3155–9.

38. Liu J, Chen S, Quan T, Wang Y, Wang O. Bone microstructure of adult

patients with non-surgical hypoparathyroidism assessed by high-resolution peripheral quantitative computed tomography. Osteoporos Int. 2020;31(11):2219–30.

39. Chawla H, Saha S, Kandasamy D, Sharma R, Sreenivas V, Goswami R. Vertebral Fractures and Bone Mineral Density in Patients With Idiopathic Hypoparathyroidism on Long-Term Follow-Up. J Clin Endocrinol Metab. 2017;102(1):251–8.

40. Laway BA, Goswami R, Singh N, Gupta N, Seith A. Pattern of bone mineral density in patients with sporadic idiopathic hypoparathyroidism. Clin Endocrinol (Oxf). 2006;64(4):405–9.

41. Chen Q, Kaji H, Iu MF, Nomura R, Sowa H, Yamauchi M, et al. Effects of an Excess and a Deficiency of Endogenous Parathyroid Hormone on Volumetric Bone Mineral Density and Bone Geometry Determined by Peripheral Quantitative Computed Tomography in Female Subjects. J Clin Endocrinol Metab. 2003;88(10):4655–8.

42. Cipriani C, Minisola S, Bilezikian JP, Diacinti D, Colangelo L, Piazzolla V, et al. Vertebral Fracture Assessment in Postmenopausal Women With Postsurgical Hypoparathyroidism. J Clin Endocrinol Metab. 2021;106(5):1303–11.

43. Hong AR, Lee JH, Kim JH, Kim SW, Shin CS. Effect of Endogenous Parathyroid Hormone on Bone Geometry and Skeletal Microarchitecture. Calcif Tissue Int. 2019;104(4):382–9.

44. Mendonça ML, Pereira FA, Nogueira-Barbosa MH, Monsignore LM, Teixeira SR, Watanabe PCA, et al. Increased vertebral morphometric fracture in patients with postsurgical hypoparathyroidism despite normal bone mineral density. BMC Endocr Disord. 2013;13(1):1–8.

45. Cusano NE, Nishiyama KK, Zhang C, Rubin MR, Boutroy S, McMahon DJ, et al. Noninvasive Assessment of Skeletal Microstructure and Estimated Bone Strength in Hypoparathyroidism. J Bone Miner Res. 2016;31(2):308–16.

46. Marcucci G, Cianferotti L, Parri S, Altieri P, Arvat E, Benvenga S, et al.

HypoparaNet: A Database of Chronic Hypoparathyroidism Based on Expert Medical-Surgical Centers in Italy. Calcif Tissue Int. 2018 Aug 6;103(2):151–63.

47. Underbjerg L, Malstroem S, Sikjaer T, Rejnmark L. Bone Status Among Patients With Nonsurgical Hypoparathyroidism, Autosomal Dominant Hypocalcaemia, and Pseudohypoparathyroidism: A Cohort Study. J Bone Miner Res. 2018;33(3):467–77.

48. Fujiyama K, Kiriyama T, Ito M, Nakata K, Yamashita S. Attenuation of postmenopausal high turnover bone loss in patients with hypoparathyroidism. J Clin Endocrinol Metab. 1995;80(7):2135–8.

49. Bilezikian JP, Silverberg SJ, Shane E, Parisien M, Dempster DW. Characterization and evaluation of asymptomatic primary hyperparathyroidism. J Bone Miner Res. 1991;6(SUPPL. 2):85–9.

50. Formenti AM, Tecilazich F, Giubbini R, Giustina A. Risk of vertebral fractures in hypoparathyroidism. Rev Endocr Metab Disord. 2019;20(3):295–302.

51. Langdahl BL, Mortensen L, Vesterby A, Eriksen EF, Charles P. Bone histomorphometry in hypoparathyroid patients treated with vitamin D. Bone. 1996 Feb;18(2):103–8.

52. Rubin MR. Skeletal Manifestations of Hypoparathyroidism. Bone. 2019;120(July 2018):548–55.

53. Rubin MR, Zhou H, Cusano NE, Majeed R, Omeragic B, Gomez M, et al. The Effects of Long-term Administration of rhPTH(1-84) in Hypoparathyroidism by Bone Histomorphometry. J Bone Miner Res. 2018;33(11):1931–9.

54. Rubin MR, Dempster DW, Zhou H, Shane E, Nickolas T, Sliney J, et al. Dynamic and Structural Properties of the Skeleton in Hypoparathyroidism. J Bone Miner Res. 2008 Dec;23(12):2018–24.

55. Sakane EN, Vieira MCC, Lazaretti-Castro M, Maeda SS. Predictors of Poor Bone Microarchitecture Assessed by Trabecular Bone Score in Postsurgical

Hypoparathyroidism. J Clin Endocrinol Metab. 2019;104(12):5795–803.

56. van Rietbergen B, Weinans H, Huiskes R, Odgaard A. A new method to determine trabecular bone elastic properties and loading using micromechanical finite-element models. J Biomech. 1995 Jan;28(1):69–81.

57. Macdonald HM, Nishiyama KK, Kang J, Hanley DA, Boyd SK. Age-related patterns of trabecular and cortical bone loss differ between sexes and skeletal sites: A population-based HR-pQCT study. J Bone Miner Res. 2011 Jan;26(1):50–62.

58. Starr JR, Tabacco G, Majeed R, Omeragic B, Bandeira L, Rubin MR. PTH and bone material strength in hypoparathyroidism as measured by impact microindentation. Osteoporos Int. 2020;31(2):327–33.

59. Underbjerg L, Sikjaer T, Mosekilde L, Rejnmark L. Postsurgical hypoparathyroidism-Risk of fractures, Psychiatric Diseases, Cancer, Cataract, and Infections. J Bone Miner Res. 2014;29(11):2504–10.

60. Pal R, Bhadada SK, Mukherjee S, Banerjee M, Kumar A. Fracture risk in hypoparathyroidism: a systematic review and meta-analysis. Osteoporos Int. 2021;

61. Fonseca H, Moreira-Gonçalves D, Coriolano HJA, Duarte JA. Bone quality: The determinants of bone strength and fragility. Sport Med. 2014;44(1):37–53.

62. Rubin MR, Dempster DW, Kohler T, Stauber M, Zhou H, Shane E, et al. Three dimensional cancellous bone structure in hypoparathyroidism. Bone. 2010;46(1):190–5.

63. Peacock M. Hypoparathyroidism and the Kidney. Endocrinol Metab Clin North Am. 2018;47(4):839–53.

64. Tay YKD, Tabacco G, Cusano NE, Williams J, Omeragic B, Majeed R, et al. Therapy of Hypoparathyroidism with rhPTH(1-84): A Prospective, 8-Year Investigation of Efficacy and Safety. J Clin Endocrinol Metab. 2019;104(11):5601–10.

65. Mannstadt M, Clarke BL, Bilezikian JP, Bone H, Denham D, Levine MA, et

al. Safety and Efficacy of 5 Years of Treatment with Recombinant Human Parathyroid Hormone in Adults with Hypoparathyroidism. J Clin Endocrinol Metab. 2019;104(11):5136–47.

66. Chen KS, Gosmanova EO, Curhan GC, Ketteler M, Rubin M, Swallow E, et al. Five-year estimated glomerular filtration rate in patients with hypoparathyroidism treated with and without rhPTH(1–84). J Clin Endocrinol Metab. 2020;105(10):e3557–65.

67. Clarke BL, Vokes TJ, Bilezikian JP, Shoback DM, Lagast H, Mannstadt M. Effects of parathyroid hormone rhPTH(1–84) on phosphate homeostasis and vitamin D metabolism in hypoparathyroidism: REPLACE phase 3 study. Endocrine. 2017;55(1):273–82.

68. Winer KK. Advances in the treatment of hypoparathyroidism with PTH 1 – 34. Bone [Internet]. 2019;120(9):535–41. Available from: https://doi.org/10.1016/j.bone.2018.09.018

69. Winer KK, Zhang B, Shrader JA, Peterson D, Smith M, Albert PS. Synthetic Human Parathyroid Hormone 1-34 Replacement Therapy : A Randomized Crossover Trial Comparing Pump Versus Injections in the Treatment of Chronic Hypoparathyroidism. J Clin Endocrinol Metab. 2012;97(2):391–9.

70. Rubin MR, Bilezikian JP. Hypoparathyroidism: clinical features, skeletal microstructure and parathyroid hormone replacement. Arq Bras Endocrinol Metabol. 2010;54(2):220–6.

71. Sikjaer T, Rejnmark L, Thomsen JS, Tietze A, Brüel A, Andersen G, et al. Changes in 3-Dimensional Bone Structure Indices in Hypoparathyroid Patients Treated with PTH(1-84): A Randomized Controlled Study. J Bone Miner Res. 2012;27(4):781–8.

72. Cipriani C, Abraham A, Silva BC, Cusano NE, Rubin MR, McMahon DJ, et al. Skeletal changes after restoration of the euparathyroid state in patients with hypoparathyroidism and primary hyperparathyroidism. Endocrine. 2017;55(2):591–8.

73. Cipriani C, Pepe J, Silva BC, Rubin MR, Cusano NE, McMahon DJ, et al. Comparative Effect of rhPTH(1-84) on Bone Mineral Density and Trabecular

Bone Score in Hypoparathyroidism and Postmenopausal Osteoporosis. J Bone Miner Res. 2018;33(12):2132–9.

74. Cusano NE, Rubin MR, Williams JM, Agarwal S, Tabacco G, Tay D, et al. Changes in Skeletal Microstructure Through Four Continuous Years of rhPTH(1–84) Therapy in Hypoparathyroidism. J Bone Miner Res. 2020;35(7):1274–81.

75. Rubin MR, Zwahlen A, Dempster DW, Zhou H, Cusano NE, Zhang C, et al. Effects of Parathyroid Hormone Administration on Bone Strength in Hypoparathyroidism. J Bone Miner Res. 2016;31(5):1082–8.

Appendix

Fact Sheet

Introduction

Hypoparathyroidism (hypoPT) is a rare disease with a **lack of two hormones, PTH and active vitamin D**. PTH **increases the level of calcium** in the blood by mobilizing calcium from bone, reducing calcium excretion in the kidney and activating vitamin D which then increases calcium uptake in the gut. HypoPT is caused by removal or damage during neck surgery (**postsurgical hypoPT) or nonsurgical** reasons (such as genetic or autoimmune diseases). The result is a low PTH level, leading to **low calcium levels** (hypocalcaemia) and **high phosphate levels** (hyperphosphatemia). Especially organs most affected by PTH, such as kidney and bone, can be damaged in the long term.

Results

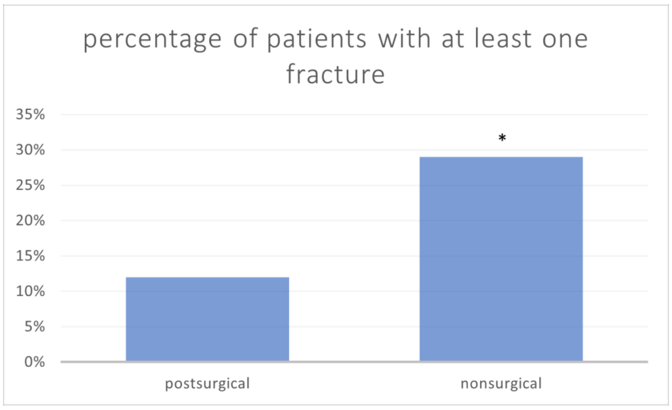
In our observational retrospective study, we assessed manifestations in kidney and bone in 191 patients with hypoPT (156 postsurgical, 35 had nonsurgical, 70% women). The patients with **postsurgical hypoPT** (mean age 65 years) were **older** than the ones with nonsurgical hypoPT (mean age 49 years).

The **renal function** was worse in patients with postsurgical hypoPT, but the group with nonsurgical hypoPT had more kidney stones.

Despite younger age, **fractures** were more likely in patients with **nonsurgical hypoPT** (29% had at least one fracture compared to only 12% of patients with postsurgical hypoPT), see figure. This was especially evident for proximal femur and other leg fractures.

Conclusion

Because there are not many people affected by this disease, we **need more research** to be able to understand and prevent longterm renal and skeletal complications.



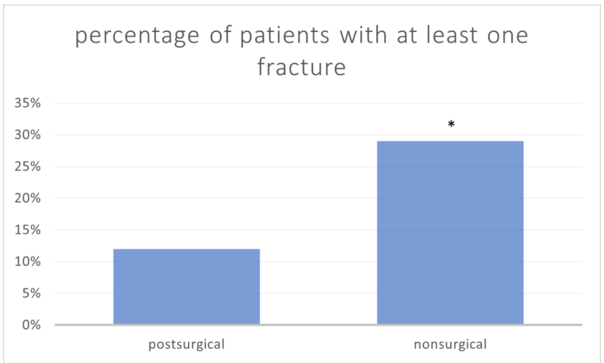
Zusammenfassung der Diplomarbeit

Einleitung

Die Nebenschilddrüsenunterfunktion (NSD-Unterfunktion; Hypoparathyreoidismus) ist eine seltene Erkrankung mit einem **Mangel an zwei Hormonen, PTH und Vitamin D**. PTH **erhöht die Menge an Kalzium im Blut**, indem es Kalzium aus dem Speicher im Knochen mobilisiert, die Kalziumausscheidung in der Niere verringert und Vitamin D aktiviert, dieses erhöht die Kalziumaufnahme im Darm, dieser kann durch eine Operation am Hals entstehen (**postoperativer Hypopara),** andere Ursachen sind zB. genetisch oder durch Autoimmunerkrankungen **(nicht-operativer Hypopara).** Durch niedrige PTH Konzentrationen kommt es zu **niedrigen Kalziumwerten** (Hypokalzämie) und **hohen Phosphatwerten** (Hyperphosphatämie). Vor allem Organe, an denen PTH besonders stark wirkt, können dabei Schaden erleiden, wie Niere und Knochen.

Ergebnisse

In unserer retrospektiven Beobachtungsstudie haben wir 191 Patient*innen mit NSD-Unterfunktion untersucht. 156 hatten eine postoperativ und 35 eine nicht-operative Erkrankung (70% Frauen). Patient*innen mit **postoperativer** NSD-Unterfunktion waren **älter** (Durchschnittsalter 65 Jahre) als die mit nicht-operativer NSD-Unterfunktion (Durchschnittsalter 49 Jahre). Die Gruppe mit postoperativer NSD-Unterfunktion hatte eine **schlechtere Nierenfunktion**, aber **Nierensteine** waren häufiger bei Patient*innen mit nicht-operativer NSD-Unterfunktion. **Knochenbrüche** waren trotz jüngeren Alters deutlich häufiger bei Patient*innen mit **nicht-operativer** NSD-Unterfunktion. (29% verglichen mit 12% der Patient*innen mit postoperativer NSD-Unterfunktion), s. Diagramm. Dieser Unterschied war besonders stark ausgeprägt bei Oberschenkelhals- und anderen Beinbrüchen.



Zusammenfassung und Ausblick

Da nicht viele Menschen von dieser Erkrankung betroffen sind, ist **noch mehr Forschung** in diesem Bereich notwendig, um die Krankheit besser zu kennen und behandeln zu können und besonders die betroffenen Organe Niere und Knochen langfristig besser schützen zu können.

Copyrights

Figure 1: Reprinted from Endocrinol Metab Clin North Am, 47 / 4, David Goltzman, Physiology of Parathyroid Hormone / Parathyroid hormone actions in kidney in regulating ion transport, 743-758., Copyright (2018), with permission from Elsevier. [OR APPLICABLE SOCIETY COPYRIGHT OWNER].

Figure 2: made by the author with Microsoft Excel

Figure 3: Reprinted from Journal of Bone and Mineral Research 23/12, John P Bilezikian et al.: Dynamic and Structural Properties of the Skeleton in Hypoparathyroidism 2018-24 (2009), with permission from John Wiley and Sons

Figure 4: Reprinted by permission from Springer Nature Customer Service Centre GmbH: Springer Nature Reviews, Endocrine and Metabolic Disorders, Risk of vertebral fractures in hypoparathyroidism, Anna Maria Formenti et al (2019)

Figure 5: reprinted under terms of Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0/) from Chen KS, Gosmanova EO, Curhan GC, Ketteler M, Rubin M, Swallow E, et al. Five-year estimated glomerular filtration rate in patients with hypoparathyroidism treated with and without rhPTH(1–84). J Clin Endocrinol Metab. 2020;105(10):e3557–65.

Figure 6: reprinted under terms of Creative Commons Attribution License (https://creativecommons.org/licenses/by/4.0/) from Mannstadt M, Clarke BL, Bilezikian JP, Bone H, Denham D, Levine MA, et al. Safety and Efficacy of 5 Years of Treatment with Recombinant Human Parathyroid Hormone in Adults with Hypoparathyroidism. J Clin Endocrinol Metab. 2019;104(11):5136–47.

Figure 7: Reprinted from Journal of Bone and Mineral Research 26/11, Mishaela R Rubin et al.: PTH(1–84) administration reverses abnormal bone-remodeling dynamics and structure in hypoparathyroidism 2727-36 (2011) with permission of John Wiley and Sons

Figure 8: made by the author with Microsoft PowerPoint

Figure 9: made by the author with Microsoft Excel

Figure 10: made by the author with Microsoft Excel

Figure 11: made by the author with Microsoft Excel

Figure 12: made by the author with Microsoft Excel

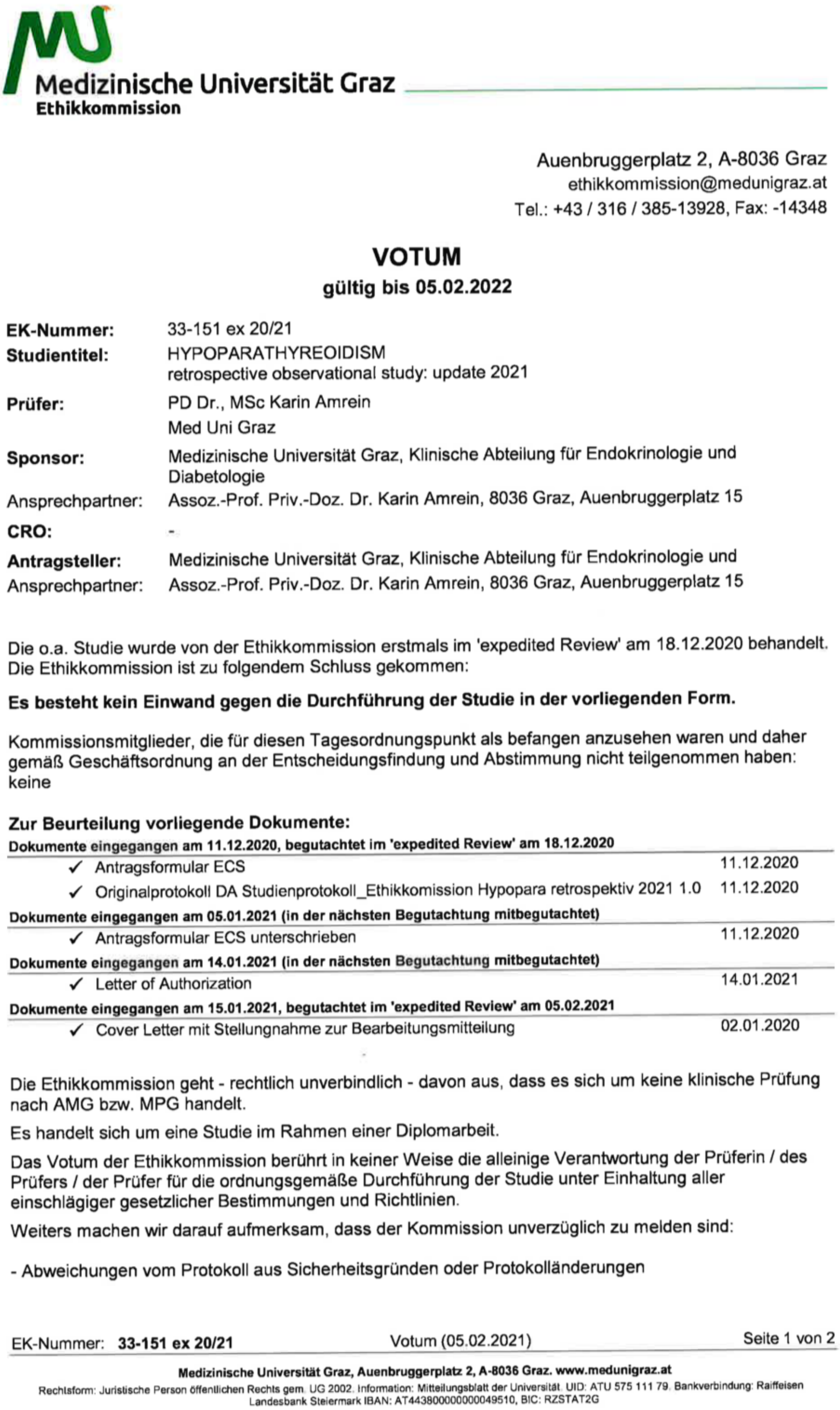
Figure 13: made by the author with Microsoft Excel

Figure 14: made by the author with Microsoft Excel

Figure 15: made by the author with Microsoft Excel

Figure 16: made by the author with Microsoft Excel

Vote of Ethics Committee



Medizinische Universität Graz
Ethikkommission

Auenbruggerplatz 2, A-8036 Graz
ethikkommission@medunigraz.at
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

- 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!