Parathyroid Hormone

Hyper- and Hypoparathyroidism Effect of Treatment and Long-term Follow-up Studies

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Gothenburg, 2024

Cover Illustration: Georgios Kontogeorgos

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ISBN: 978-91-8069-415-5 (PRINT)
ISBN: 978-91-8069-416-2 (PDF)

http://hdl.handle.net/2077/79095

Printed by Stema Specialtryck AB, Borås, Sweden, 2023

To my beloved family, Silvana, Maria and Lara

ABSTRACT

Background: High or low parathyroid hormone (PTH) can be challenging in diagnosis and treatment. The prevalence and natural history of normocalcemic hyperparathyroidism (nHPT) are still not known. The knowledge gap regarding fracture risk, other comorbidities, and mortality in nHPT in the population is deep. Hypoparathyroidism (HypoPT) is the only endocrine disease for which there is no substitution of the missing hormone, PTH. A fraction of the natural PTH, teriparatide (PTH 1-34), is used in the treatment of severe osteoporosis.

Aims and methods: The aim was to study the prevalence of fractures, morbidity, and mortality in individuals with nHPT and HypoPT. The self-reported Health-Related Quality of Life (HRQoL) for patients with HypoPT compared with age-matched controls from the population was studied with validated generic questionnaires, the EuroQol-5 dimensions visual analogue scale and the Short Form-36. The effects on bone, fractures and HRQoL of daily administration of teriparatide (PTH 1-34) were investigated in patients with severe osteoporosis in comparison with the population and a placebo-treated control group with osteoporosis during 10 years of follow-up.

The hypothesis was that nHPT in men and women from the population would lead to higher morbidity and mortality and that HRQoL was low in patients with HypoPT and osteoporosis but improved in osteoporotic patients treated with teriparatide.

Results: nHPT was common in the population, up to 11%, and did not progress to primary hyperparathyroidism (pHPT) up to 21 years later. No increase in comorbidity or mortality was observed in nHPT. Subjects with HypoPT had lower HRQoL, fewer fractures and no increased morbidity or mortality in comparison with the population. One out of five patients with HypoPT would benefit from other treatment than the calcium and active vitamin D therapy traditionally used. Teriparatide increased bone mineral density and decreased fracture frequency up to 10 years after treatment start. HRQoL was low in osteoporotic women and did not improve with treatment.

Conclusion: The newly described clinical phenotype, nHPT, was common in the population but did not lead to pHPT, more fractures or higher morbidity or mortality during up to 21 years of follow-up. HRQoL was low in subjects with HypoPT and in women with severe osteoporosis. Teriparatide had an anabolic effect on osteoporotic bone and favorable effect on fractures after 10 years but HRQoL was unaffected.

Keywords: Calcium, Hyperparathyroidism, Hypoparathyroidism, Vitamin D, Population, Fractures, Cardiovascular disease, Quality of Life, Comorbidity, Teriparatide, Osteoporosis

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SAMMANFATTNING PÅ SVENSKA

Primär hyperparatyreoidism (pHPT) karakteriseras av högt kalcium i blodet och högt bisköldkörtelhormon, paratyreoideahormon (PTH), och är den tredje vanligaste endokrina sjukdomen efter diabetes mellitus och hypotyreos och vanligast hos kvinnor efter menopausen. Njursten och frakturer är vanligt vid pHPT.

Sedan PTH-metoden introducerades på 1990-talet har även en ny, okänd typ av hyperparatyreoidism (HPT) med normal kalk- och vitamin D-halt i blodet HPT (nHPT) beskrivits. Detta tillstånd är i regel symtomfritt. Förekomsten är okänd liksom utvecklingen av tillståndet avseende pHPT och övrig sjuklighet.

Slumpmässigt valda män och kvinnor ur befolkningen följdes upp till 21 år avseende sjukdomar och dödsorsak. nHPT var vanligt, 2%, och ökade till 11% med stigande ålder. Ingen ökning av frakturer, hjärtkärlsjukdom eller död konstaterades efter upp till 21 års uppföljning. Ingen utvecklade pHPT.

Den enda botande behandlingen av pHPT är halsoperation. Efter detta finns en risk för låg produktion av PTH och en sällsynt sjukdom, hypoparatyreoidism (HypoPT). Tillståndet behandlas traditionellt med kalcium och D-vitamintabletter. Kontrollen av sjukdomen kan bli svår eftersom man inte ersätter det hormon som fattas i kroppen. Behandling med PTH-ersättning finns nu tillgänglig.

Förekomsten av HypoPT var 0,02% och 203 personer besökte läkare på Sahlgrenska Universitetssjukhuset mellan 2007 och 2022. Deras självskattade livskvalitet var låg i jämförelse med övriga befolkningen i Göteborg. Ingen ökad förekomst av frakturer eller hjärtkärlsjukdom sågs. Baserat på livskvalitet och svårreglerad kalciumhalt i blodet uppskattades cirka 20% av alla med HypoPT vara i behov av den nya substitutionsbehandlingen med PTH 1–84.

PTH-behandling i form av teriparatid (PTH 1–34) under två år hos kvinnor med svår benskörhet ledde till bättre benmassa och färre frakturer efter tio år. Livskvaliteten var låg och påverkades inte av PTH-behandlingen.

Man kan konstatera efter 21 års uppföljning att nHPT är vanligt i befolkningen men inte farligt. HypoPT är sällsynt, förenat med låg livskvalitet och det finns ett behov av hormonersättning. Behandling med teriparatid minskade risken för frakturer men lyckades inte återställa livskvaliteten vid svår osteoporos.

LIST OF PAPERS

The thesis is based on the following studies/published papers, referred to in the text by their Roman numerals:

I. Kontogeorgos G, Trimpou P, Laine CM, Oleröd G, Lindahl A, Landin-Wilhelmsen K. Normocalcaemic, vitamin D-sufficient hyperparathyroidism - high prevalence and low morbidity in the general population: A long-term follow-up study, the WHO MONICA project, Gothenburg, Sweden.
Clin Endocrinol (Oxf). 2015 Aug; 83(2):277-84. doi: 10.1111/cen.12819. Epub 2015 Jun 15.

II. Kontogeorgos G, Welin L, Fu M, Hansson PO, Landin-Wilhelmsen K, Laine CM. Hyperparathyroidism in men - morbidity and mortality during 21 years' follow-up.
Scand J Clin Lab Invest. 2020 Feb; 80(1):6-13.
doi:10.1080/00365513.2019.1683763. Epub 2019 Nov 13.

III. Kontogeorgos G, Mamasoula Z, Krantz E, Trimpou P, Landin-Wilhelmsen K, Laine CM. Low health-related quality of life in hypoparathyroidism and need for PTH analog.
Endocr Connect. 2022 Jan 10; 11(1): e210379. doi: 10.1530/EC-21-0379.

IV. Kontogeorgos G, Krantz E, Trimpou P, Laine CM, Landin-Wilhelmsen K. Teriparatide treatment in severe osteoporosis - a controlled 10-year follow-up study.
BMC Musculoskelet Disord. 2022 Nov 24;23(1):1011. doi: 10.1186/s12891-022-05987-2.

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CONTENT

ABBREVIATIONS

BMD	Bone Mineral Density
BMI	Body Mass Index
DXA	Dual-energy X-ray Absorptiometry
EQ5D-VAS	EuroQol-5 Dimensions Visual Analogue Scale
GH	Growth Hormone
HPT	Hyperparathyroidism
HRQoL	Self-reported Health-Related Quality of Life
HRT	Hormone Replacement Treatment
HypoPT	Hypoparathyroidism
IOM	Institute of Medicine
nHPT	Normocalcemic vitamin D sufficient Hyperparathyroidism
pHPT	Primary Hyperparathyroidism
PTH	Parathyroid Hormone
PTH 1-34	Teriparatide
PTH 1-84	Recombinant human parathyroid hormone
PTX	Parathyroidectomy
S-1,25$(OH)_2$D	Serum 1,25-dihydroxy-vitamin D
S-25(OH)D	Serum 25-hydroxy-vitamin D
S-Ca	Serum total Calcium
S-Ca ion	Serum ionized Calcium
SD	Standard Deviation
SF-36	Short Form-36
sHPT	Secondary Hyperparathyroidism
S-PTH	Serum Parathyroid Hormone
WHO	World Health Organization
WHO MONICA	World Health Organization MONItoring trends and determinants in CArdiovascular disease

INTRODUCTION

History

The human parathyroid gland was first described by the Swedish medical student Ivar Sandström (Figure 1) in Uppsala in 1877, and is the latest anatomically discovered gland (1). Sandström's description of his finding of the "small pea", in his article "On a New Gland in Man and Several Animals" in the publication "Uppsala Läkareförenings Förhandlingar" in 1880 (1), was the start of the understanding of the function and importance of the parathyroid gland. He named the glands "glandulae parathyroideae" and this name remains unchanged until today (2).

Figure 1. Ivar Sandström 1852-1889. The Upsala Journal of Medical Sciences, 2015; 120: 72-77, (1). With permission.

The physiology and pathophysiology of the new organ was unknown. It was observed that tetany and death often occurred after a thyroidectomy, but that these outcomes were not seen when the parathyroid glands were preserved in canine experiments (2). In 1924, it was discovered that tetany was a result of low calcium levels and could be treated with injections of parathyroid extract (2). It was not until late July 1925 in Vienna that the first successful parathyroidectomy (PTX) was performed on a patient with a previous femur

fracture and very high blood calcium levels. Before the curative operation, with the identification and surgical removal of the hyperplasic parathyroid gland, this patient was unsuccessfully treated with parathyroid extract injections that worsened his symptoms. The initial treatment approach demonstrates the incomplete understanding of parathyroid disorders at this time (2).

Thanks to the new imaging techniques we use today, the size, anatomical position, and individual variations in the position of the parathyroid glands can often be identified. Modern laboratory methods and the knowledge we have today help us understand that the pathological observations described in the past were the result of very low/absent or very high concentrations of serum parathyroid hormone (S-PTH).

The use of the multichannel autoanalyzer in the 1970s increased the possibility to identify primary hyperparathyroidism (pHPT), *i.e.,* high calcium and high PTH in the blood, before the severe clinical manifestations of the disease (kidney stones, fractures, psychical symptoms). As the analysis of the serum total calcium (S-Ca) was easy to perform asymptomatic patients with mild hypercalcemia were identified at routine screening. The introduction of methods that measure S-PTH with high accuracy, the most recent in use being the second and third generation methods, led to the discovery of a new, previously unknown category of patients with elevated S-PTH but normal S-Ca. This state, with no secondary cause of S-PTH elevation, has been denoted normocalcemic hyperparathyroidism (nHPT) (3).

Physiology

Parathyroid hormone (PTH) is produced and stored in the four parathyroid glands situated in the neck and has a key function in calcium metabolism (4) (Figure 2). PTH secretion is mainly regulated by the calcium concentrations in the blood (Figure 3). The calcium levels in the circulation play a very important role for vital organ functions, such as heart contraction and heart rate, as well as muscle contraction and all calcium-mediated functions in the body. The maintenance of stable S-Ca is achieved mainly with the interaction of PTH, the kidneys, the skeleton, vitamin D, and the bowel (4). A reduction in calcium at the extracellular level stimulates calcium-sensing receptors (CaSR) from the parathyroid gland within seconds and, as a result, PTH is eliminated from the circulation. PTH binds to the parathyroid receptors 1 in the kidney, which results

in increased distal tubular reabsorption of calcium. The same receptors are found in the bones and bowel. In the skeleton, the main body reserve of calcium, PTH stimulates osteoclasts, which results in the release of the calcium from the bone. PTH stimulates the increase of serum 1,25-dihydroxy-vitamin D (S-$1,25(OH)_2D$), which is the active hormone of the serum 25-hydroxy-vitamin D (S-25(OH)D), and that results in higher absorption of calcium from the gut (5) (Figure 3). Another type of PTH receptors, parathyroid receptors type 2, are identified in the brain and bowel but their functions are still unknown (5). PTH-related peptide is produced by the placenta and the breasts during pregnancy and lactation from cartilage and other organs. PTH-related peptide is not a hormone and is not regulated by S-Ca but has the same affinity for the parathyroid receptor 1 as PTH and can induce hypercalcemia (5, 6).

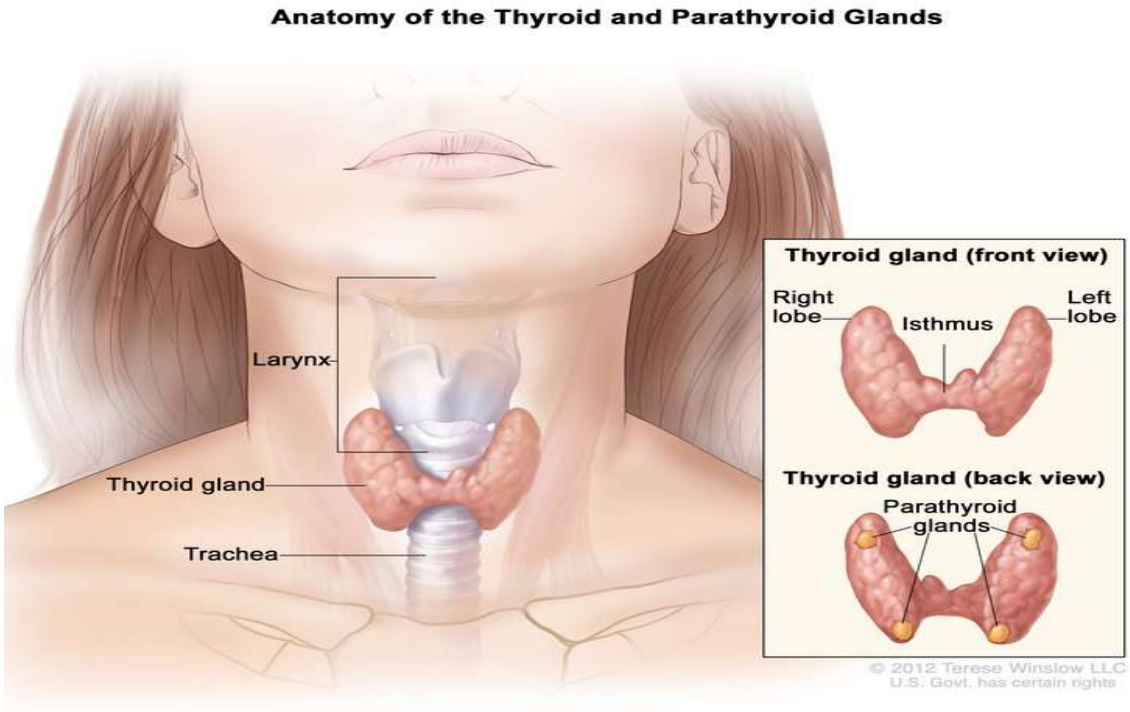


Figure 2. Anatomy of the Thyroid and Parathyroid Glands. For the National Cancer Institute © (2012). Terese Winslow LLC, U.S. Govt. has certain rights. With permission.

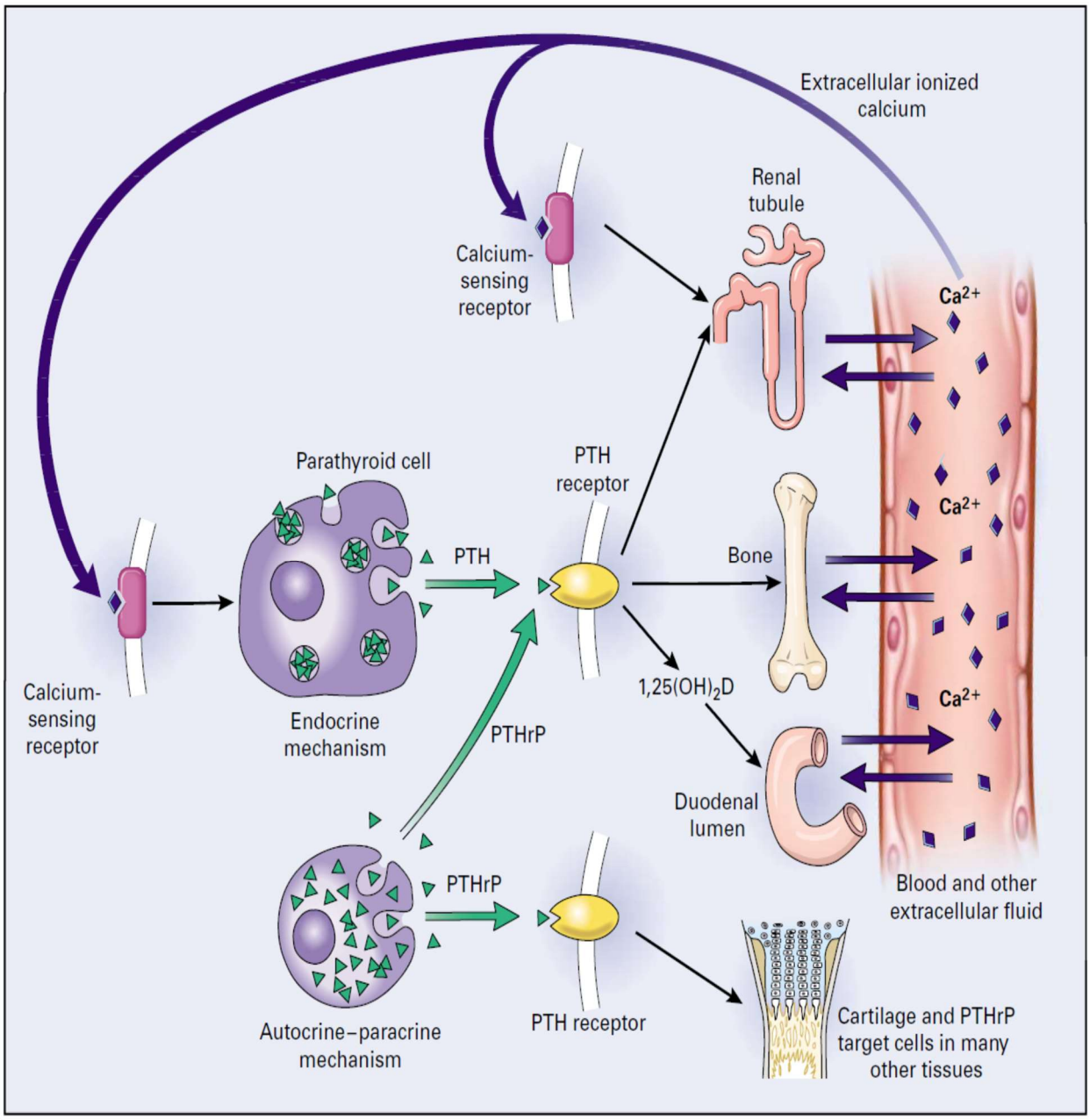


Figure 3. The parathyroid axis. The synthesis of parathyroid hormone (PTH) and parathyroid hormone-related peptide (PTHrP) is shown on the left, and their target sites of action are shown on the right. Both act by means of the same receptor (parathyroid receptor 1). Blue arrows indicate extracellular calcium flow. Reproduced with permission from (Marx SJ. Hyperparathyroid and hypoparathyroid disorders. The New England Journal of Medicine. 2000;343(25):1863-75), (5). Copyright Massachusetts Medical Society.

Definitions

Primary hyperparathyroidism (pHPT)

The combination of high S-Ca and elevated or inappropriately normal levels of S-PTH was defined as primary hyperparathyroidism (pHPT) (7) (Table 1). pHPT is the third most common endocrine disorder after diabetes mellitus and hypothyroidism (4). The prevalence of pHPT was 2.1% in postmenopausal Scandinavian women aged 55 to 75 years (8). The prevalence of pHPT in men was previously estimated to 0.7% (9). In general, women are affected 3-4 times more often than men and the prevalence increases with age (10).

Normocalcemic hyperparathyroidism (nHPT)

During the Third International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism in 2008, a new phenotype of parathyroid disorder, considered similar to asymptomatic pHPT, was officially described: normocalcemic, vitamin D sufficient hyperparathyroidism (nHPT) (11). This disorder was defined as constantly elevated S-PTH with maintained normal S-Ca concentrations in the absence of secondary causes of elevated PTH (11) (Table 1). The prevalence of the newly described phenotype is not known. The definition of the disorder has changed from the time it was first described until today (Table 2).

Secondary hyperparathyroidism (sHPT)

Secondary hyperparathyroidism (sHPT) is defined as low levels of S-Ca and elevated value of S-PTH (12), (Table 1). The most common cause of sHPT is vitamin D deficiency. The cut-off level of S-25(OH)D proposed as sufficient by the Institute of Medicine (IOM) was 50 nmol/L (13), but Holick et al. recommended a concentration above 75 nmol/L (14). Other conditions that may lead to sHPT are low calcium intake, renal calcium loss due to kidney disease, kidney insufficiency (eGFR < 60 mL/min), malabsorption and medication (15).

Hypoparathyroidism (HypoPT)

Hypoparathyroidism (HypoPT) is defined as low S-Ca levels in the presence of undetectable/low or inappropriate low normal concentrations of S-PTH (16), (Table 1). HypoPT in adults is usually iatrogenic (75%) and caused by devascularization or removal of the parathyroid glands during neck surgery for thyroid diseases or PTX. Other causes of HypoPT are genetic, due to gene mutations (ex. GCM2, PTH, CASR, GNA11), as part of a syndrome [ex. Di-George (22q11-deletion syndrome), Kenny-Caffey type 1 and type 2], idiopathic, autoimmune or metabolic disorders such as hypermagnesemia or severe hypomagnesemia, which occur in about 25% of cases (15, 16). The prevalence of HypoPT is estimated to 10-24 cases per 100,000 inhabitants in different studies (17-19), with only 2/100,000 cases of HypoPT classified as non-iatrogenic (20). Postoperative HypoPT can be transient or permanent (chronic). According to the clinical guidelines of the European Society of Endocrinology, chronic HypoPT is considered when the HypoPT persists more than six months postoperatively (16). In accordance with the guidelines from the Second International Workshop on Parathyroid Disorders in 2022, the period of persistent postoperative HypoPT was extended to more than twelve months to be considered as chronic (21).

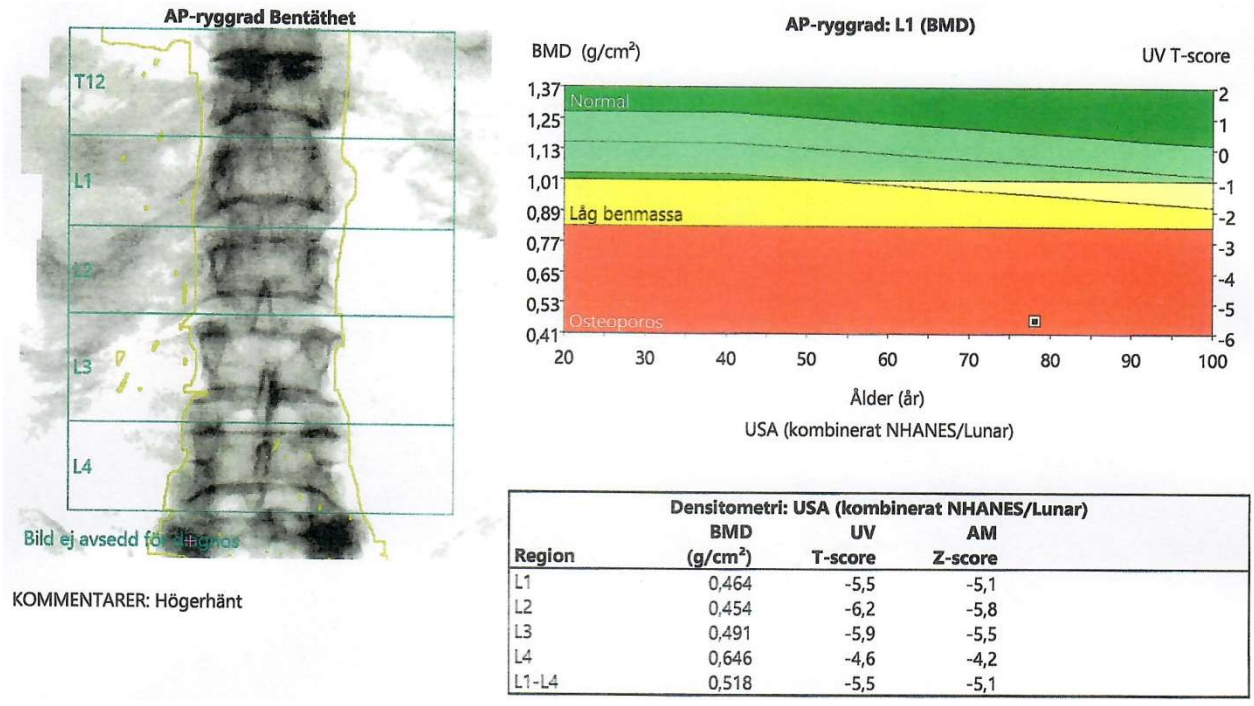
Table 1. Association between parathyroid disorders and serum total calcium (S-Ca), serum ionized calcium (S-Ca ion), serum 25-hydroxy-vitamin D (S-25(OH)D) and serum parathyroid hormone (S-PTH).

	S-Ca	S-Ca ion	S-25(OH)D	S-PTH
Hyperparathyroidism (HPT)	N ↑↓	N ↑↓	N ↑↓	↑
Primary Hyperparathyroidism (pHPT)	↑	↑	N ↑↓	↑
Normocalcemic Hyperparathyroidism (nHPT)	N	N	N	↑
Secondary Hyperparathyroidism (sHPT)	↓	↓	N ↓	↑
Hypoparathyroidism (HypoPT)	↓	↓	N	N ↓

N: normal levels; ↓: low levels; ↑: high levels; Reference: (7, 11-13, 16)

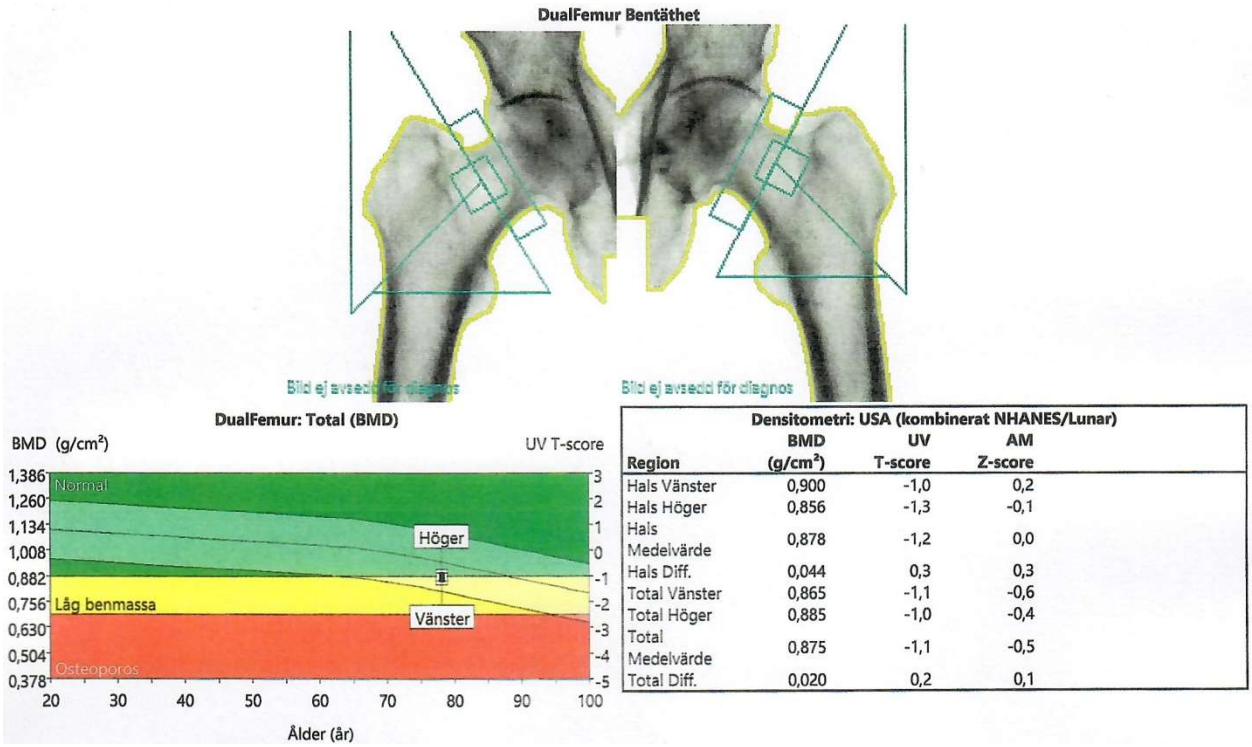
Osteoporosis

According to the World Health Organization (WHO), the definition of osteoporosis is based on the measurement of Bone Mineral Density (BMD) and the standard deviation (SD) of BMD from the average value for young healthy women, expressed as the T-score. Different reference populations are used in defining the T-score, depending on the country and/or ethnicity, and this is the reason why measurements in patients with osteoporosis may differ internationally, making it difficult to compare studies. An adult with a T-score < -2.5 SD in one or more measured sites, femoral neck or spine, is diagnosed with osteoporosis (22). BMD is measured with Dual energy X-ray Absorptiometry (DXA) (Figures 4 a, b). Subjects with osteoporosis have a higher risk of fragility fractures but other factors such as sex, age, family history of hip fracture, high fall risk, low Body Mass Index (BMI), medication (often glucocorticoids), previous fragility fracture, smoking, and alcohol consumption influence the fracture risk (22).



Densitometri: USA (kombinerat NHANES/Lunar)			
Region	BMD (g/cm²)	UV T-score	AM Z-score
L1	0,464	-5,5	-5,1
L2	0,454	-6,2	-5,8
L3	0,491	-5,9	-5,5
L4	0,646	-4,6	-4,2
L1-L4	0,518	-5,5	-5,1

Figure 4a. Illustration of Dual-energy X-ray Absorptiometry (DXA) of the spine and the measurements performed. AP: anteroposterior; BMD: bone mineral density; L: lumbar; UV: young adult; AM: age-matched.



Densitometri: USA (kombinerat NHANES/Lunar)			
Region	BMD (g/cm²)	UV T-score	AM Z-score
Hals Vänster	0,900	-1,0	0,2
Hals Höger	0,856	-1,3	-0,1
Hals Medelvärde	0,878	-1,2	0,0
Hals Diff.	0,044	0,3	0,3
Total Vänster	0,865	-1,1	-0,6
Total Höger	0,885	-1,0	-0,4
Total Medelvärde	0,875	-1,1	-0,5
Total Diff.	0,020	0,2	0,1

Figure 4b. Illustration of Dual-energy X-ray Absorptiometry (DXA) of the femur and the measurements performed. BMD: bone mineral density; UV: young adult; AM: age-matched.

Dual-energy X-ray Absorptiometry (DXA)

DXA is a radiological method used internationally to measure BMD, determine bone strength and, together with other clinical tools, such as the fracture risk assessment algorithm, estimate the risk of bone fractures. DXA is the gold standard used in the diagnosis and monitoring of osteoporosis (Figures 4 a, b).

Other clinically relevant measurements offered by DXA are body composition, vertebral fracture assessment assisting in the diagnosis of vertebral fractures, and the trabecular bone score as a predictor of vertebral fractures, especially in elderly patients (23). The dose of X-rays used during a DXA scan is estimated to 0.2% of the annual background radiation that the population is exposed to or a chest X-ray. This makes it possible to use DXA in the diagnosis and follow-up of osteoporosis without serious safety considerations (23).

To assure a high quality of the examination, the DXA machine has to be calibrated regularly. The placement of the patient in the right position is important and, preferably, the same DXA scan with the same software should be used to allow for comparison between patients and their previous examinations. The T-score and the Z-score are used to diagnose osteoporosis.

The T-score and the Z-score

The T-score is the value expressing the difference between the patient's BMD and the expected BMD value of an average healthy adult divided with the SD of the healthy population (24). The T-score used in Sweden is based on the WHO definition and uses BMD from an adult white female population between 20 and 40 years old. A T-score $\geq$ -1 is defined as a normal skeleton, between -1 and -2.5 as lower than the skeleton in a normal healthy population or osteopenia, while a T-score < -2.5 is defined as osteoporosis and a T-score of < -2.5 associated with at least one fragility fracture is considered severe osteoporosis (24) (Figures 4 a, b).

The Z-score is similar to the T-score, but the measured BMD is compared with that in healthy individuals matched for age, sex, weight and race, according to the WHO definition. The Z-score is often used to compare BMD measurements in premenopausal women, in men below the age of 50 and in children (25).

Osteoporotic fractures

An osteoporotic, or fragility, fracture is defined as a fracture sustained with low energy trauma, often after a fall from standing height or less (26). The most frequent sites of osteoporotic fractures are the hip and the spine but other sites, such as the proximal humerus, the distal forearm, the clavicle, the scapula, the rib, and the bones of the distal leg may be the site of the first fragility fracture (26) Figure 5.

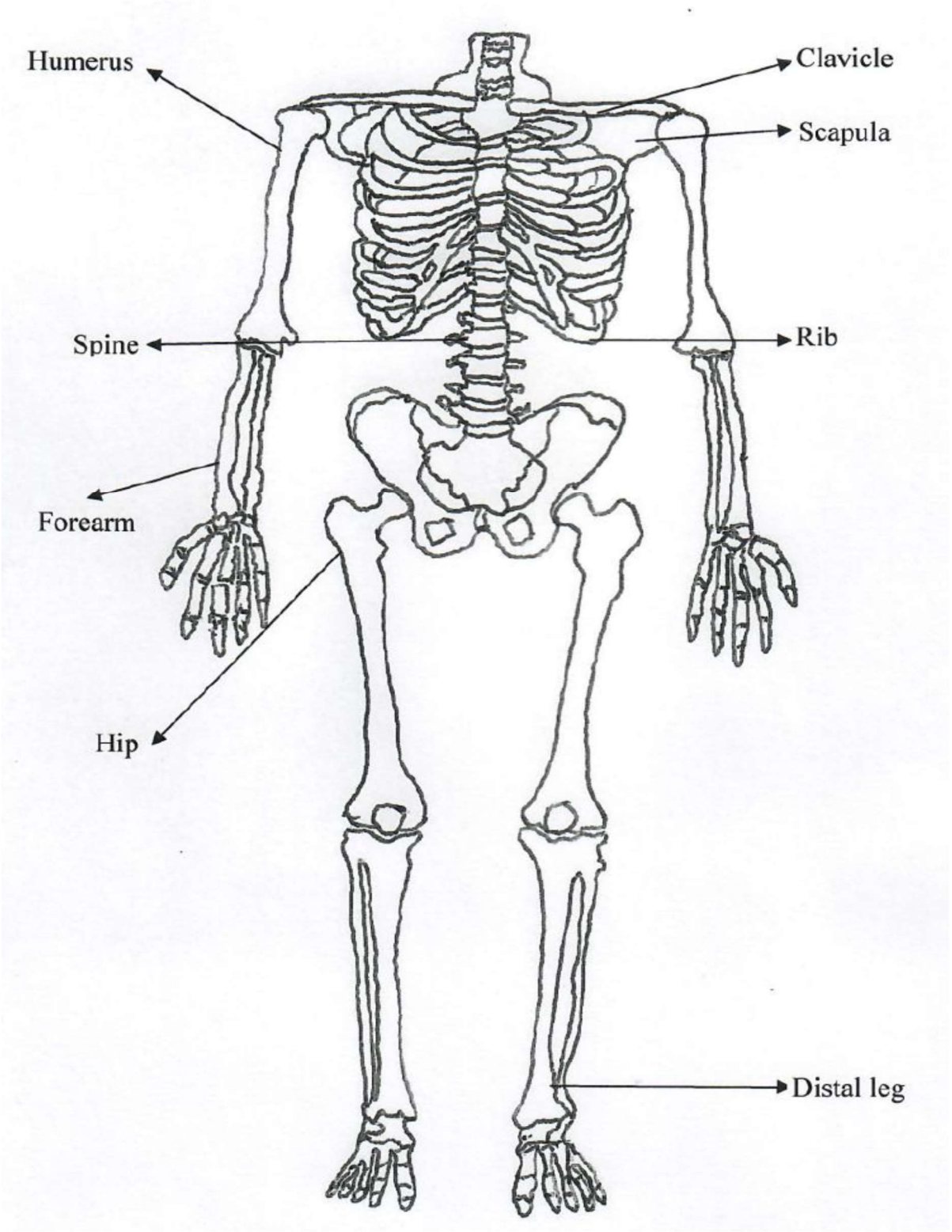


Figure 5. Possible sites of osteoporotic fractures in the human skeleton.

Self-reported Health-Related Quality of Life (HRQoL)

The definition of self-reported Health-Related Quality of Life (HRQoL) is still not as clear as the definition of health status described by WHO in 1948 (27). HRQoL often describes the effect on the function of a subject by a medical condition or its treatment perceived by the patient (28). There are generic and disease-specific questionnaires to quantify HRQoL, depending on the study population and the outcome studied. The Short Form-36 (SF-36) and the EuroQol-5 Dimensions Visual Analogue Scale (EQ5D-VAS) questionnaires are two of the most commonly used validated generic instruments to measure patient HRQoL (28).

Pathophysiology and clinical manifestations of Parathyroid Hormone disorders

Primary hyperparathyroidism (pHPT)

In pHPT, the PTH overproduction results in hypercalcemia. pHPT is often due to the hypertrophy of one (85%) or more (15%) parathyroid glands and rarely a carcinoma (1%) (4). The clinical manifestations of pHPT vary from serious, with hyperparathyroid bone disease, bone loss and fractures, and nephrocalcinosis, kidney stones, kidney function impairment, neuromuscular and neuropsychiatric manifestations (stones, bones, groans and psychic moans) (Figure 6), to asymptomatic patients who are accidentally discovered during usual laboratory investigations (3). It is important to investigate rigorously the possibility of other diagnoses with similar biochemical findings, such as Familial Hypocalciuric Hypercalcemia (type 1, type 2 or type 3), Multiple Endocrine Neoplasia (1, 2 A or 4), Hyperparathyroidism-Jaw Tumor syndrome and familial isolated hyperparathyroidism, which have another treatment approach than pHPT (15).

In addition to the classic affections of the bones and the kidneys in pHPT, manifestations from other organs and even increased mortality have been associated with the disease (29).

In the cardiovascular system, high S-PTH was associated with hypertrophy of the myocardial cells that could lead to left ventricular hypertrophy, inotropic effects on the heart, increasing heart rate and elevated coronary blood flow (30, 31). Increased arterial stiffness was also associated with high S-PTH levels (32). An association between pHPT and high blood pressure, diabetes mellitus, insulin resistance and lipid metabolism has been described (33, 34). The impact of the asymptomatic forms of pHPT and nHPT, which has been considered a part of asymptomatic pHPT, on different organs, mortality, and disease management in patients with asymptomatic disease is not clear.

Normocalcemic hyperparathyroidism (nHPT)

Two main hypotheses were developed for the pathophysiology of nHPT. The first suggested that an elevated S-PTH level was a result of the resistance in the action of PTH in the bone and the kidneys (35). The second theory considered that nHPT was the subclinical phenotype of pHPT, where only the S-PTH levels were high in that phase and the disorder develops to pHPT with hypercalcemia in a second phase (36). Based on the biphasic theory and referral subjects, it was concluded that many, but not all subjects with nHPT, will most probably develop hypercalcemia and pHPT (3). Three international workshops and two European group meetings were conducted with experts on parathyroid disorders, to answer the questions of what the natural history is and how clinicians should determine the diagnosis and treat patients with asymptomatic pHPT and especially nHPT (11, 15, 37-39). The questions remain unanswered, and more studies are needed to identify the prevalence and natural history of nHPT, to form reliable guidelines and clarify existing recommendations (40) (Table 2). The latest international guidelines underline the importance of excluding any other conditions that may lead to misclassification of a secondary hyperparathyroidism (sHPT) to nHPT (15, 39). The national guidelines in Sweden, available since April 2023 (41), recommend considering an nHPT diagnosis in subjects with normal S-Ca ion with kidney stones or other manifestations that can be associated with pHPT. The only condition was to exclude other causes of an elevated S-PTH.

Table 2. Comparison in the approach of normocalcemic hyperparathyroidism (nHPT) from the time first described until today. S-PTH: serum parathyroid hormone; S-Ca: serum total calcium; S-Ca ion: serum ionized calcium; S-25(OH)D: serum 25-hydroxy-vitamin D; HRQoL: Self-reported Health Related Quality of Life; pHPT: primary hyperparathyroidism; PTX: parathyroidectomy. N: normal; ↓: low ; ↑: high.

	S-PTH	S-Ca total	S-Ca ion	Measure albumin-adjusted S-Ca, S-PTH	S-25(OH)D	Other	Blueprints for future research
2008 3rd International Workshop (11)	↑	N	N	No specific recommendations.	> 50	Secondary causes of ↑S-PTH excluded.	Natural history and pathophysiology.
2014 4th International Workshop (37)	↑	N	N	At least 3 values over 3-6 months.	> 50 (> 75)	Secondary causes of ↑S-PTH excluded.	Natural history and pathophysiology.
2018 1st European Society of Endocrinology Workshop PARAT (42)	↑	N	N	At least 3 values over 3-6 months.	> 75	Secondary causes of ↑S-PTH excluded. Administer vitamin D and/or calcium for several weeks before definitive diagnosis.	Natural history of fractures, cardiovascular risk and HRQoL in pHPT.
2021 ESE Educational program of Parathyroid disorders PARAT (15)	↑	N	N	At least 3 values over 3 months. Retest S-PTH 3-6 months after calcium repletion or thiazide challenge test. S-PTH may be high 12 months after vitamin D	> 75	Secondary causes of ↑S-PTH excluded. Administer vitamin D and/or calcium for several weeks before definitive diagnosis. " Thiazides challenge"	Natural history of fractures, cardiovascular risk and HRQoL in pHPT and nHPT.
2022 5th International Workshop (39)	↑	-	N	At least 2 values over 3-6 months.	> 75	Secondary causes of ↑S-PTH excluded	Global definition, incidence, prevalence, natural history with/without PTX, genetic forms.

Secondary hyperparathyroidism (sHPT)

The most common cause of sHPT is vitamin D insufficiency. Hence, it is important to measure 25-(OH)D levels when S-Ca is low. However, there are cases of sHPT where the S-Ca levels are normal as a result of the stimulation by the high PTH levels (12). Those findings can lead to sHPT being misclassified as nHPT. The level of S-25(OH)D proposed as sufficient by the IOM in 2011 was 50 nmol/L (13). The cut-off levels of S-25(OH)D proposed by the latest guidelines as sufficient, when considering the diagnosis of nHPT, was > 75 nmol/L (Table 2) (15, 39). When S-25(OH)D is below 75 nmol/L, new testing of S-PTH after 3-6 months is recommended after treatment with vitamin D supplementation (15).

Low S-Ca levels may be a result of low calcium intake or low absorption in the bowel. In many cases, the patient's medical history can provide valuable information for the diagnosis by dietary questionnaires, information about bariatric surgery, lactose intolerance, celiac disease or inflammatory bowel disease. Laboratory investigation with transglutaminase antibodies and gastroscopy to exclude celiac disease, or fecal calprotectin to exclude inflammatory bowel disease, may be necessary to exclude other causes than low dietary intake (15). The treatment of the underlying disease and/or the increase in calcium intake can normalize S-Ca and S-PTH levels.

Also, kidney disease may be a cause of low S-Ca levels by two mechanisms, renal calcium loss and kidney insufficiency. During increased renal calcium excretion, the levels of S-Ca decline, which stimulates the increase in S-PTH. Kidney insufficiency, defined as eGFR < 60 mL/min, leads to increased calcium loss, lower 1,25-$(OH)_2$D, less calcium absorption from the bowel and higher levels of S-PTH. Thiazide diuretics can be used to reverse increased calciuresis (15).

Some medications may also cause sHPT (lithium, loop diuretics, antiepileptics, antiresorptives, SGLT2 inhibitors, proton pump inhibitors, glucocorticoids) (12, 15).

Hypoparathyroidism (HypoPT)

In chronic PTH deficiency, the mechanisms that are PTH-mediated cannot maintain physiological levels of calcium in the blood. A lack of PTH leads to diminished stimulation of the renal reabsorption of calcium and the production of $1,25(OH)_2D$ in the kidney. This, in turn, decreases the calcium absorption from the bowel and the calcium from the skeleton is not mobilized. As a result, calcium levels in the blood remain low (Table 1). Depending on the S-Ca levels, S-Ca level variations and individual adaptation mechanisms, the symptoms can vary from mild, such as fatigue, "brain fog," paresthesia around the mouth and the extremities, and muscle cramps of small muscle groups, to more serious, such as seizures or even life-threatening symptoms like laryngospasm (5) (Figure 6). In the absence of PTH, phosphate reabsorption from the kidney is not inhibited and the phosphate accumulates in the body. Relative hypercalciuria is often also present (43). Standard treatment with oral calcium supplementation and active vitamin D generally results in almost normal levels of S-Ca but even greater elimination of the calcium from the kidneys. All these conditions, in the absence of the regulating function of PTH, were suggested as the cause of the high risk of nephrocalcinosis, kidney stones and progressive kidney impairment (43). HypoPT has been shown to be associated with abnormal bone turnover, but with apparently normal BMD, as well as calcifications of other organs such as basal ganglia and the risk of cataract (44).

The "patient presentation matrix" was proposed by HypoPT experts as a classification method to divide patient treatment control using biochemical levels and the patient´s described well-being (Figure 7) (45). The use of this classification was mainly of academic interest at the time it was proposed as there were few treatment options but underlined the need for other treatment strategies in HypoPT, preferably hormone substitution. The approval of the recombinant human parathormone (PTH 1-84) in 2015 in the United States, for the treatment of both postoperative and non-postoperative HypoPT was described as the start of a new era in the medical management of HypoPT (46).

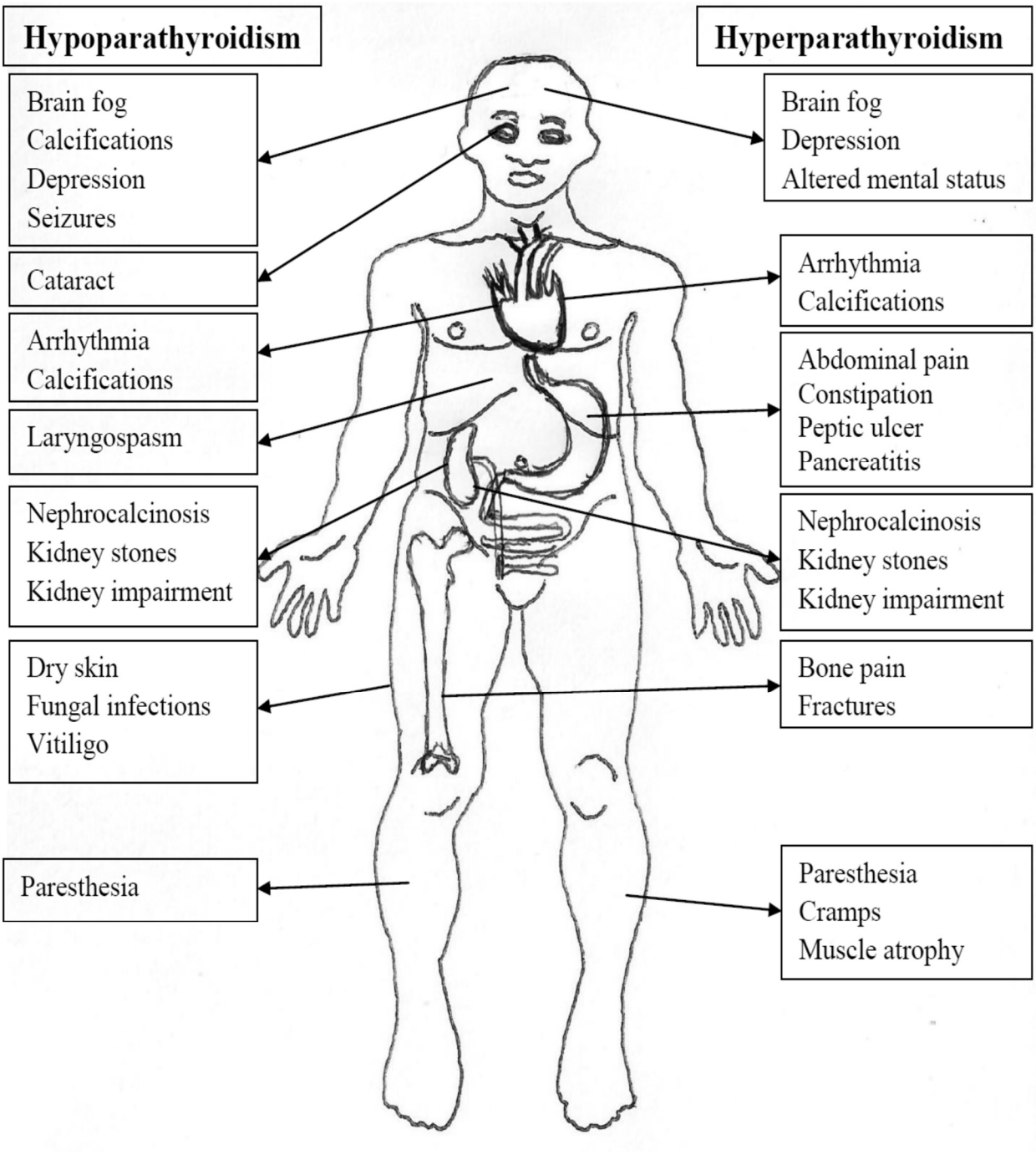


Figure 6. Presentation of the most common signs and symptoms of hypoparathyroidism and hyperparathyroidism related to body systems.

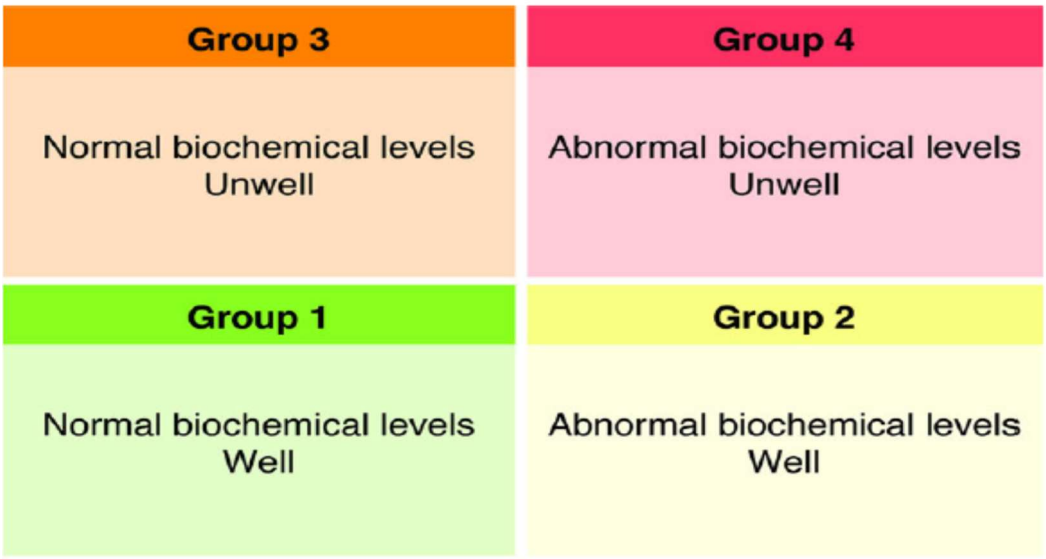


Figure 7. Patient wellness based on the severity of hypoparathyroidism-related symptoms, comorbidities and complications in relation to biochemical levels. Reproduced with permission from Iqbal K (Defining the Characteristics of Chronic Hypoparathyroidism Not Adequately Controlled on Conventional Therapy: Consensus Findings of Three European Delphi Panels. Advances in therapy. 2019;36(11):3007-16.) Advance in Therapy (45).

PTH treatment

Recombinant human parathyroid hormone (PTH 1-84)

Recombinant human parathyroid hormone (PTH 1-84) is a drug identical to the entire PTH molecule length with 84 amino acids (Figure 8). After subcutaneous administration of PTH 1-84 the drug reaches its maximum concentration after 5-30 minutes with another peak concentration after one to two hours. Its half life depends on the dose and is approximately three hours and the calcium-raising effect in the blood persists more than 24 hours. Even the effect on the kidneys related to calcium reabsorption and phosphate elimination is up to 24 hours from the administration of one dose. This makes it possible to administer the drug once daily.

There are no clinical guidelines with well-defined recommendations for the use of PTH 1-84, but experts suggest the use of PTH 1-84 in subjects who are not well controlled with conventional treatment and experience many symptoms and low HRQoL (47).

A problem in PTH 1-84 treatment is the subcutaneous administration, which is a barrier for many patients. The treatment is under restriction and monitoring as rats developed osteosarcoma, a form of bone cancer, in a study with another recombinant parathyroid hormone, teriparatide (16). Another problem is that PTH 1-84 was withdrawn in Sweden in 2022 and the only available recombinant PTH; however, without the indication to treat HypoPT, is teriparatide.

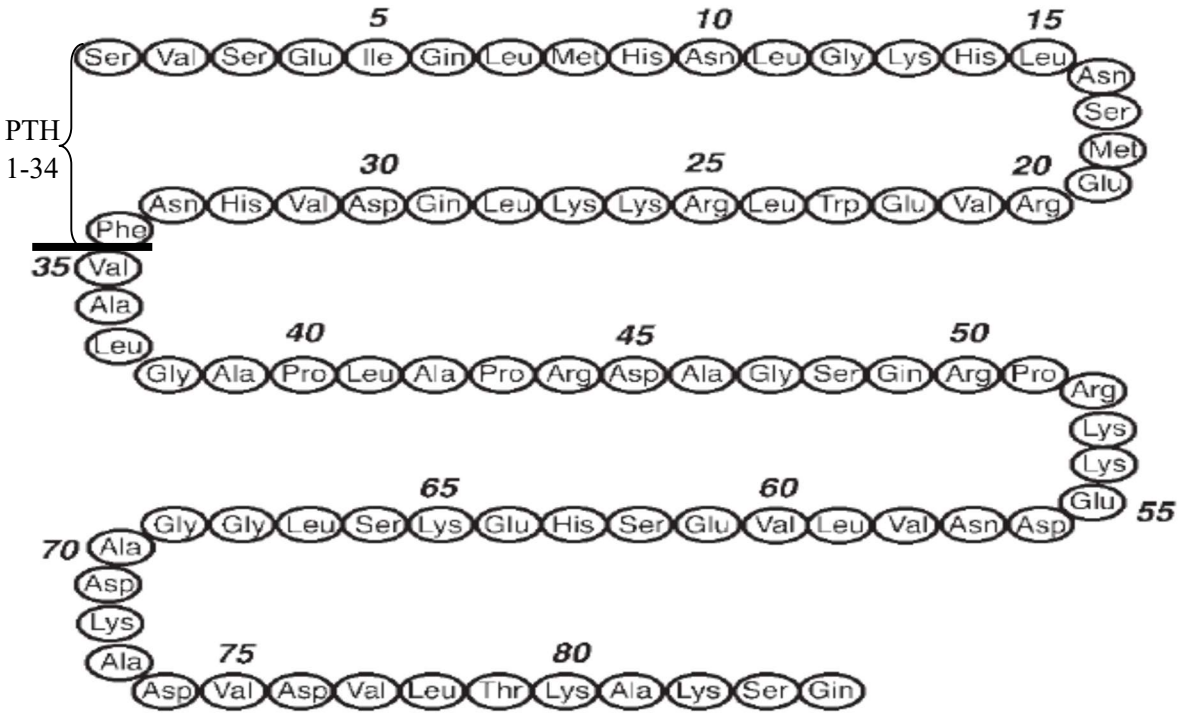


Figure 8. Human parathyroid hormone demonstrating the full length PTH (1-84) and the first 34 amino acids of PTH (1-34). Figure modified from Sarah P. Shrader and Kelly R. Ragucci. Parathyroid hormone (1-84) and treatment of osteoporosis. Ann Pharmacother. 2005; 39: 1511–16, (48). With permission.

Teriparatide (PTH 1-34)

Teriparatide is another recombinant human PTH that comprises the first 34 amino acids (PTH 1-34) of the full-length 84-amino acids peptide (Figure 8) (49). Teriparatide, was also used as substitution treatment in HypoPT in some studies but was not approved for this indication. The short half life of PTH 1-34, one hour, and the need for more than one daily injection to maintain stable S-Ca concentrations, seem to be the reasons for the non-approval (50-52). An anabolic effect on the bone was observed in those studies (51) (Figure 9).

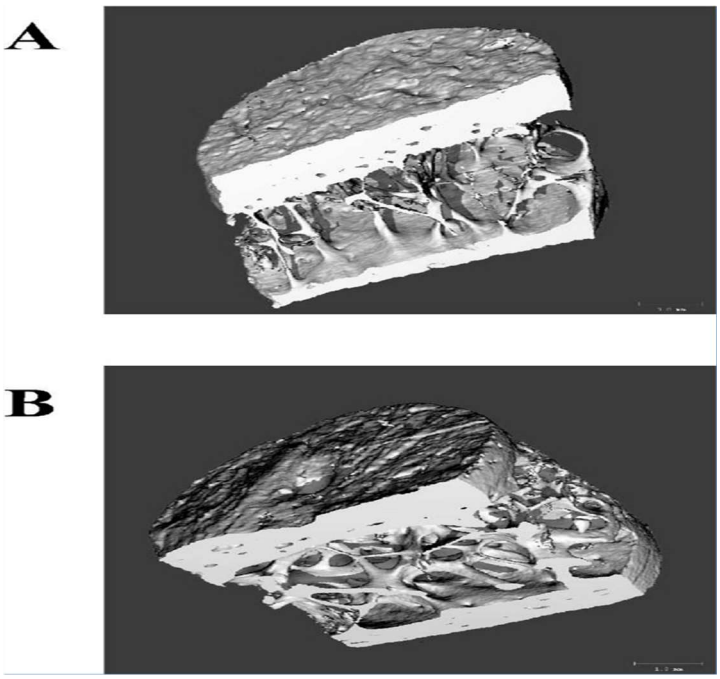


Figure 9. Effects of parathyroid hormone treatment on vertebral bone mass via bone biopsy. A: Baseline, B: after 21 months of treatment of a 65-year-old woman. Jiang, Y., Zhao, J.J., Mitlak, B.H., Wang, O., Genant, H.K. and Eriksen, E.F. (2003), Recombinant Human Parathyroid Hormone (1–34) [Teriparatide] Improves Both Cortical and Cancellous Bone Structure. J Bone Miner Res, 18: 1932-1941, (53). With permission.

In 2001, Neer et al. presented a randomized, multinational, multicenter, placebo-controlled study with teriparatide in postmenopausal women with osteoporosis and at least one vertebral fracture. The subjects received daily injections with placebo, teriparatide 20 μg or teriparatide 40 μg subcutaneously for a median observation time of 21 months. An increase in BMD at the level of the lumbar spine of 9% and 13% was observed, as well as an increase at the femoral neck level of 3% and 6%, with the doses of 20 μg and 40 μg, respectively, compared with placebo (54). The risk of new vertebral fractures was also significantly reduced (54). The study was stopped earlier than planned, because of the development of osteosarcoma in rodents during routine toxicological studies with teriparatide. For safety reasons, those findings limited the indication for treatment with teriparatide in humans, first to 18 months and later to 24 months once in a lifetime (55, 56). The use of bisphosphonate is recommended to preserve the bone gained after completing the teriparatide treatment (49). Since teriparatide was approved, the risk of osteosarcoma was not found to be higher in individuals treated with teriparatide in comparison with the population, according to the results reported from an ongoing long-term safety study (57).

Osteoporosis treatment and HRQoL

Patients with osteoporosis have an increased risk of fractures, resulting in higher comorbidity and mortality (58). The risk of a new osteoporotic fracture is high after a fragility fracture (59).

The first-line treatment in osteoporosis is an oral or intravenous bisphosphonate. As an alternative, subcutaneous denosumab is recommended (26). In patients with a high risk of fractures, anabolic treatment with teriparatide (PTH 1-34) may be considered (22). Osteoporotic fractures, especially those of the hip and spine can be devastating and diminish HRQoL in patients (60).

The impact of a fragility fracture is high, and many subjects suffer from chronic pain, disability, and limitations in everyday life. As a result, HRQoL is seriously affected and the effect of the treatment on HRQoL has become an important endpoint in clinical trials (59). Many questionnaires were developed in order to estimate treatment effect, and both generic and disease-specific scales are used. In many studies presenting short-term data on teriparatide treatment, the EQ5D-VAS was used to evaluate HRQoL (59-65). The long-term effect after teriparatide treatment on fractures and HRQoL is not known.

Treatment with PTH and knowledge gaps

Treatment with recombinant human PTH is an attractive option, both in osteoporosis due to the anabolic effect on the bone, and as substitution therapy in HypoPT.

The lack of long-term controlled studies in treatment with teriparatide in real-life conditions, with hard endpoints such as fractures, is a problem. Other aspects of the treatment, such as HRQoL compared with individuals of similar age as controls, a long time after the treatment are also of interest, both for patients and physicians.

PTH treatment in HypoPT seems to be more physiologic than the present standard treatment with active vitamin D and calcium substitution. Conventional treatment aims to maintain S-Ca levels at physiological and stable levels, with the risk of hyper- and hypocalcemia, but does not affect the phosphate levels, calciuria and bone turnover (66). Many attempts have been made to use recombinant human PTH 1-34 as substitution therapy. PTH 1-34 was used with promising results in studies as subcutaneous injection once daily, twice daily or as an infusion with the use of insulin pumps, but the treatment was not approved for the management of HypoPT (51, 52, 67). The investigational drug, TransCon PTH (palopegteriparatide) is a prodrug of PTH 1-34 (68). It has been shown in phase 3 clinical trials that once daily subcutaneous administration of TransCon PTH can maintain normal and stable calcium concentrations without the need for calcium and active vitamin D substitution. Normalization of the phosphate concentration and calciuria as well as improved HRQoL were also observed (69). TransCon PTH is not approved for the treatment of HypoPT and the treatment costs, the stability of the drug and the recommended treatment duration are unknown.

To reduce the discomfort and increase the compliance with the treatment, intranasal administration (70, 71) or administration with a transdermal teriparatide patch were also studied (72, 73), but none of those administration modalities are as yet available.

Last but not least, the knowledge gap is due to there being limited interest in research on patients with HypoPT. The reason has probably been the low prevalence of HypoPT and the variety of clinical manifestations. Furthermore, we have had no hormone replacement or new treatment to offer in studies of this patient group, which may have limited researcher interest. HypoPT has several

and variable causes, which makes it difficult to design long-term, randomized controlled trials for the study of hard endpoints, such as fractures or other morbidities and mortality, or other important disease-related affections such as HRQoL. Hence, until today, observational, real-world controlled studies, offer valuable information in the understanding of the risks of the disease and the unmet needs of the patients. This thesis was aimed to describe such an overview based on clinical experience.

AIMS

The overall aim of this thesis was to study the effects of high/inappropriately high and absent, low, or inappropriately low S-PTH on fractures, morbidity, and mortality. Another aim of the thesis was the effect of intermittent administration of PTH in patients with severe osteoporosis, as daily subcutaneous injections of 20 μg PTH 1-34 (teriparatide), on fractures, other morbidity and HRQoL (Table 3).

The specific aims and hypothesis of the thesis by paper were:

Paper I: The primary aim was to estimate the prevalence of HPT in general, and nHPT in particular, and the evolution of the new clinical phenotype, nHPT, over 13 years in a random population sample of men and women. Secondary aims were to investigate whether morbidity and mortality up to 17 years in subjects with nHPT were higher than in subjects with normal S-PTH levels in the same population.

The hypothesis was that nHPT would lead to pHPT and that any subjects with HPT, irrespective of S-Ca, would have a higher risk of fractures, more cardiovascular events and high morbidity and mortality during the long-term follow-up period.

Paper II: The prevalence of all types of HPT, irrespective of S-Ca levels, was studied as well as the outcome of fractures, cardiovascular morbidity, and overall mortality of all types of HPT in men of the same age (50 years old at start) during a 21-year follow-up period.

The hypothesis was that men in the general population with HPT had a higher risk of fractures, cardiovascular morbidity, and mortality than those without HPT.

Paper III: HRQoL and morbidity were studied in HypoPT in comparison with the background population and the need for treatment with a PTH analog was estimated.

The hypothesis was that patients with HypoPT had lower HRQoL and higher morbidity compared with the general population. The second hypothesis was that those with fluctuations in S-Ca, mainly challenging hypocalcemia, would benefit the most from PTH supplementation.

Paper IV: The effect of teriparatide (PTH 1-34) treatment for up to two years in women with severe osteoporosis followed for a total of ten years was studied and the effects on HRQoL and fractures compared with the placebo group from another study, "The growth hormone study" (74), and a population sample, respectively, during the same period were compared.

The hypothesis was that teriparatide improved HRQoL and lowered the risk of new fractures.

MATERIAL AND METHODS

Table 3. The participants, study design, statistics, and outcome of paper I-IV. nHPT: normocalcemic, vitamin D sufficient, hyperparathyroidism; S-PTH: serum parathyroid hormone; BMI: body mass index; HPT: hyperparathyroidism; HypoPT: hypoparathyroidism; PTH 1-84: recombinant human parathyroid hormone; HRQoL: self-reported Health-Related Quality of Life, ↓: low, ↑: high.

	Women n (%) **Men n (%)**	**Age (years)** **Mean (SD)**	**Method/** **Design**	**Statistics**	**Outcome**
Paper I	419 (69) 189 (31)	49 (10) Range 25–64	Case control Longitudinal 13-17 years Retrospective	Students t test Mann-Whitney test Fisher's exact test Logistic regression	Prevalence of nHPT: 2-11% S-PTH correlated positively with age, BMI, treated hypertension. nHPT did not lead to pHPT or increased morbidity or mortality
Paper II	0 (0) 750 (100)	50 (0)	Cohort study Longitudinal 21 years Retrospective	Students t test Fisher's exact test Cox regression	Prevalence of nHPT: 2.8% No increase in fractures, cancer, cardiovascular disease or mortality in those with HPT
Paper III	162 (80) 41 (20)	60 (20) Range 19–95	Cross-sectional Retrospective 13 years Controlled	Mann-Whitney test Fisher's exact test Two-tailed t test	Prevalence of HypoPT: 2.1% Fractures were ↓ in HypoPT, no increase in mortality. HRQoL was ↓ in HypoPT 20% of patients may benefit from PTH 1-84
Paper IV	40 (100) 0 (0)	69 (11) Range 31–81	Open-label treatment study Prospective 10 years Controlled	Paired t test Man-Whitney test Fisher's exact test	Fractures ↓ to similar rates as in the population after teriparatide HRQoL was ↓ and not affected by teriparatide

Study population

Paper I

A random population sample of 1200 men and 1200 women aged 25-64 years, from the same city, (Gothenburg, Sweden) was examined in 1995 as part of the multinational World Health Organization MONItoring trends and determinants in CArdiovascular disease the (WHO MONICA) project.
Anthropometric variables, blood sampling for hormonal analysis and bone measurements were performed in every fourth woman aged 25-44 years, all women between 45-64 years and every fourth man aged 25-64, resulting in 608 randomly selected subjects. Fractures and ongoing pharmacological treatment were also registered.
Subjects who were alive were invited 13 years later (2007-2008) for a reinvestigation. Of 608 subjects, 410 participants completed the follow-up study (67%). Data on cardiovascular morbidity and overall mortality were retrieved from medical records via the National Board of Health and Welfare, Stockholm, Sweden, 17 years later (until January 1, 2013).

Paper II

The local population register in Gothenburg, Sweden, was used to invite a randomly selected cohort of 50-year-old men in 1993 to a health examination, within the framework of the "Study of Men Born in 1943" project (75). Of the 1463 men invited, 798 (55%) agreed to participate in the study and 750 had a complete biochemical analysis and were included in the present study. Ninety-seven per cent of them were Caucasians.

The Swedish Hospital Discharge Registry and the National Board of Health and Welfare, Stockholm, Sweden, were used to collect data on previous diagnoses, morbidity, and mortality for all men in the study during 21 years (until December 31, 2014). Ongoing and previous medication as well as lifestyle factors and smoking habits were registered.

Paper III

The hospital records of the Sahlgrenska University Hospital, Gothenburg, Sweden, the largest referral center in the western region of Sweden, of nearly 800,000 inhabitants, were used to identify patients with the diagnosis of chronic HypoPT. Subjects having the potential diagnosis of HypoPT between 2007 and 2020 were identified according to the International Classification of Diseases, version 10 (ICD 10). Due to the lack of a specific ICD 10 code, which includes every kind of HypoPT and the different clinical manifestations of HypoPT, the codes E20 HypoPT, E83.5 disorders of the calcium metabolism and E89.2 postoperative HypoPT, were used in the initial identification process. The medical records of all patients, n = 814 (Table 4), were reviewed by the same endocrinologist and patients who fulfilled the diagnosis criteria for chronic HypoPT according to the definition described by the European Society of Endocrinology (16) were included in the study, n = 203. Of the 203 with chronic HypoPT of various origin, 164 were alive in 2020 and 106 answered (65%) the questions in the posted questionnaires. The answered HRQoL and fracture questionnaires were compared with a random population sample from the WHO MONICA cohort, n = 414, of similar age and sex distribution.

Table 4. ICD codes used to include patients with hypoparathyroidism in Paper III. According to ICD-10 codes, n = 814 had a probable hypoparathyroidism diagnosis of which only n = 203 fulfilled the diagnosis criteria for chronic hypoparathyroidism.

Disease	**ICD-10 Codes**	**n = 814**	**n = 203**
Hypoparathyroidism, unspecified	E20.9	64	33
Idiopathic hypoparathyroidism	E20.0	35	19
Pseudohypoparathyroidism	E20.1	11	1
Other hypoparathyroidism	E20.8	9	5
Disorders of the calcium metabolism	E83.5	590	44
Postprocedural hypoparathyroidism	E89.2	105	101

Paper IV

Patients, n = 40, women with a mean age of 69 ± 11 years, with severe osteoporosis and at least one vertebral compression were consecutively included in a prospective, open-labeled treatment study from 2004 until 2013, in real-world conditions, at the Sahlgrenska University Hospital Endocrine Outpatient Clinic. The patients were referred from other specialists based on severe osteoporosis. All women received 20 μg teriparatide subcutaneously daily for 14-24 months. Patients were followed by the same endocrinologist annually for ten years. Twenty patients completed the ten-year follow-up period and their HRQoL, DXA scans and fractures were registered at treatment start, treatment stop and after three and ten years. The results of the study were compared with DXA scans and fractures in a placebo-treated group (n = 25) from a cohort of 80 women with osteoporosis who participated in a randomized, double-blind placebo-controlled treatment study with another anabolic hormone treatment, growth hormone (GH) and ten years' follow-up (74). Women in the GH study were divided into three treatment arms; high-dose GH, low-dose GH and placebo subcutaneously daily. Only the placebo-treated group, who received placebo injections for 1.5 years, was used in the comparison with teriparatide treatment. HRQoL and fractures from the teriparatide treatment study were also compared with n = 233 age-matched, randomly selected women from the WHO MONICA population study in Gothenburg who were followed in parallel.

Methods

Anthropometry

Body weight was measured to the nearest 0.1 kg, in the morning before breakfast at every examination, in light clothing without shoes. Body height was measured in the same conditions to the nearest 1 cm. By using body weight in kilograms divided by height in meters squared, the body mass index (BMI) was calculated and expressed in kg/m². Waist and hip circumference were measured with a soft tape to the nearest 1 cm and the waist/hip ratio was calculated. The midway between the lowest rib margin and the iliac crest was measured for waist circumference and the widest part of the gluteal region was measured for hip circumference. All measurements were performed with the subjects in the standing position.

The mean of three consecutive blood pressure measurements with a random zero sphygmomanometer (Hawksley & Sons) in the sitting position after at least three minutes rest was recorded for Papers I and II. The last recorded blood pressure and anthropometrical variables were used in Paper III.

Biochemistry

Paper I: Venous blood samples were collected both at start and at follow-up 13 years later in the morning in the fasting state from January to December 1995, with the exception of July and August, and were equally distributed. Menstruating women left blood samples on cycle day 7-9. S-25(OH)D was measured with a radioimmunoassay 125I RIA kit (Liaison, DiaSorin, Stillwater, MN, USA). S-25(OH)D $\geq$ 50 nmol/L was considered as sufficient levels of vitamin D. S-1.25$(OH)_2$D was also determined with a 125I RIA kit (DiaSorin). S-PTH was determined by immunoradiometric assay (Nichols Institute Diagnostics, San Juan Capistrano CA, USA). A level of S-PTH $\geq$ 60 ng/L was defined as HPT. S-Ca in the interval 2.15 – 2.49 mmol/L was considered as normal. S-Osteocalcin was determined by radioimmunoassay. S-free T4 and S-TSH were measured with the ECLIA Modular immunometric method (Roche, Manheim, Germany). Thyroperoxidase antibodies (S-anti-TPO), vitamin B12, S-Ca, S-creatinine, S-cystatin C, lipids, serum alkaline phosphatase (S-ALP), phosphate, from serum, glucose and homocysteine from plasma were analyzed by routine methods in the accredited laboratory at Sahlgrenska University Hospital. Similar methods were used at start and follow-up.

Paper II: Fasting blood samples were collected in the morning from an antecubital vein between February 1993 and June 1994, but not in July and August 1993. Calcium, albumin, creatinine, glucose, and lipids, all from serum, were analyzed shortly after collection according to routine methods at the accredited laboratory of Sahlgrenska University Hospital. Low Density Lipoprotein (LDL) was calculated with Friedewald's estimation (76). Blood samples were stored at -80°Celsius for later analysis. The frozen blood samples were used for analysis of S-25(OH)D with a radioimmunoassay 125I RIA kit (Liaison, DiaSorin, Stillwater, MN, USA) and S-PTH with an immunoradiometric assay (Roche Cobas, Rotkreuz, Switzerland). S-Ca was albumin-corrected by using the formula 0.019 x (46 – S-Albumin) + S-Ca (77).

The reference intervals for albumin-corrected S-Ca were 2.15-2.49 mmol/L, for S-PTH 1.6-6.9 pmol/L and for S-25(OH)D $\geq$ 50 nmol/L (vitamin D sufficiency).

Paper III: Hospital medical records were used to register the most recent S-Ca, S-Ca ion, S-PTH, S-25(OH)D, S-T4 and S-TSH. S-Ca was analyzed with photometry, S-Ca ion with ion-selective electrodes, S-PTH with immuno-radiometric assay (Roche Cobas, Rotkreuz, Switzerland) and S-25(OH)D with a radioimmunoassay 125I RIA kit (Liaison, DiaSorin, Stillwater, MN, USA).

Paper IV: Blood samples were drawn in the morning in the fasting state. S-Ca, S-Ca ion, S-PTH and S-Osteocalcin were taken before medical appointments. The same methods as in Paper III were used for S-Ca, S-Ca ion and S-PTH. S-Osteocalcin was determined by radioimmunoassay.

Medical history and medication

Paper I: Similar questionnaires for the registration of ongoing medical treatment were used at the clinical examination in 1995 and 2008. All medications were coded according to the Anatomical Therapeutic Chemical Classification System (ATC). Fragility fractures verified by X-ray, cardiovascular events and death were registered. The ICD 10 codes S22, S32, S42, S52, S62, S72, S82, S92, T08, T10, T12, and T14 were used for fracture identification.

Paper II: Ongoing medical treatment was registered, and drugs were coded according to the ATC Classification System. Diagnostic codes were retrieved from the Swedish Hospital Discharge Registry and ICD codes 8, 9 and 10 were translated to ICD 10 before data analysis. Kidney stones, hypertension, neck operation, radiologically verified fractures, myocardial infarction, stroke and cancer were registered.

Paper III: The hospital medical records were used to register ongoing medication and doses, comorbidities and complications that might be related to HypoPT and its treatment, such as clinically or radiologically identified renal stones and laboratory-confirmed renal failure. For fracture identification, questionnaires completed by patients, medical records and X-ray documentation were used to confirm and complete the available data.

Paper IV: All patients participating in the treatment study with teriparatide had severe osteoporosis and at least one vertebral compression at inclusion. Ongoing medication, especially bone-specific treatment such as bisphosphonates, and bone-affecting treatments such as corticosteroids and hormone replacement therapy (HRT), and the medical status of all women were also registered at each hospital visit. All patients were prescribed teriparatide 20 µg/day subcutaneously (Figure 10) for up to 24 months and 1000 mg calcium and 800 IU cholecalciferol daily. All were examined with a DXA scan at start and after 1.5, 3 and 10 years from treatment start.

Patients treated with GH or placebo in a previous randomized, placebo-controlled study with a similar purpose (68) had DXA-verified osteoporosis and HRT at inclusion and received calcium and cholecalciferol in doses of 750 mg and 400 IU daily. They were followed with lumbar X-rays and DXA scans at start and after 1.5, 3 and 10 years (74). Fractures were registered at every examination through medical records for up to ten years (78).

Figure 10. Teriparatide injection (FORSTEO®) prescribed in Sweden. Image owned by Professor Kerstin Landin-Wilhelmsen; MD, PhD. Printed with permission.

Fractures

All previous and incidental fractures during the follow-up were verified by X-ray and documented at each medical appointment. Fractures were registered through medical records for the WHO MONICA population study until 2020. The fractures of possible osteoporotic origin were registered as ICD-10 codes (rib: S22, vertebra: S32, upper arm: S42, radius: S52, hand: S62, hip: S72, lower leg: S82, foot: S92, and vertebral compression: M48.5) and compared with fragility fractures from the teriparatide-treated group. Osteoporotic fractures from the placebo group in the GH study (74, 78) were also used for comparison with the teriparatide-treated group to compare the effect of a similar subcutaneous intervention.

Dual-energy X-ray Absorptiometry (DXA)

All patients were examined with DXA at start and after completing the treatment with teriparatide or placebo at the Sahlgrenska University Hospital DXA laboratory, Gothenburg.

The LUNAR DPX-L; Lunar Radiation Inc., Madison WI, USA, was used in the first examinations performed in 2004-2014. In 2015, the DXA scan was changed to GE Medical Systems, Lunar Corp., Madison, WI, USA, with the use of iDXA hardware, and was used for the ten-year follow-up DXA (Figure 11).

Figure 11. Photograph of DXA scanner at the Sahlgrenska University Hospital laboratory. Private photo with the permission of Sahlgrenska University Hospital.

Questionnaires

Two validated HRQoL questionnaires were used in the studies, the SF-36 and the EQ5D-VAS. The EQ5D-VAS is divided in two sections. The first section evaluates the patient's health status with the help of five questions with three severity grades in limitation of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression (79). The severity of their status can be classified as no problems, some problems, and severe problems. The second part, the Visual Analogue Scale (VAS) evaluates the patients' subjective feeling of their health status with a single question and a scale graded from 0 to 100 mm, where 0 represents the worst imaginable and 100 the best imaginable health. The SF-36 is a more complex questionnaire with 36 questions covering eight domains: physical functioning, role limitations due to physical health problems, bodily pain, general health, vitality, social functioning, role limitations due to emotional health problems, and mental health. After creating two summary measures out of the eight domains-the physical component summary and the mental component summary-with the use of the SF-36 software, a score that can be used to compare groups was calculated (80).

Subjects from the WHO MONICA population responded to the SF-36 and a single question in the EQ5D-VAS (only the VAS section) in 2007-2008 (used for comparison in Papers III and IV). Patients with HypoPT answered both the SF-36 and the complete version of the EQ5D-VAS (Paper III), and patients in the teriparatide treatment group answered both sections in the EQ5D-VAS (Paper IV).

Statistical methods

Conventional methods were used to calculate means and standard deviations, medians, and min/max. A p value less than 0.05 was considered statistically significant in all papers.

Paper I: For comparison between groups, Fisher's exact test was used for dichotomous variables. The Mantel-Haenszel Chi-square test was used for ordered categorical variables and the Mann-Whitney test for continuous variables. The Chi-square test was used to calculate the odds ratio. The t test was used for comparison of means in normally distributed parameters. Logistic regression analysis was performed to adjust for age and BMI. The SAS software

was used by a professional statistician to perform the main calculations, and also proposed and advised on the appropriate statistical methodology.

Paper II: Student's t test was used for continuous variables and Fisher's exact test for dichotomous variables. Cox regression analysis with maximum likelihood estimation to calculate the risk of fracture, comorbidities, and death in subjects with high S-PTH but normal adjusted S-Ca and S-25(OH)D, *i.e.*, patients with nHPT. Survival estimates were presented as Hazard Ratios (HR) with 95% CI. Adjustment for BMI was also performed. The same statistician using the same SAS software performed the main calculations.

Paper III: The SPSS statistics version 26 (IBM, NY, USA) and R statistics were used to calculate means, medians, standard deviations, interquartile ranges, and ranges. Fisher's exact test was used for dichotomous variables and the two-tailed t test for comparison between groups. For non-parametric variables, the Mann-Whitney test was the appropriate method for statistical comparisons.

Paper IV: The paired t test was considered the proper method to calculate differences among the same patients between two different periods of time (start and follow-up). Non-parametric variables were compared with the Mann-Whitney test. Fisher's test was used for comparison between groups in dichotomous variables. The SPSS statistical program, version 26 (IBM, NY, USA), was used. Different groups were compared with the Chi-square test with Yates correction.

Ethical considerations

The studies comply with the Declaration of Helsinki and were approved by the Ethics Committee. All participants gave their written informed consent. The National and Regional Ethics Committee in Sweden and the University of Gothenburg approved the study according to the following approval numbers:

Paper I+III+IV (The WHO MONICA study): Reg. No. 244-94, approved in 1994, Reg. No. 088-06, approved in 2006, and Reg. No. T282-11, approved in 2011.

Paper II (The Study of Men Born in 1943): Reg. No. 1993:157-93, approved in 1993, and T529-15, approved in 2015. The study was also registered in Clinical Trials.gov, Identifier: NCT 03138122.

Paper III (The HypoPT study): Reg. No. 2020: 2019-05852, approved in 2020.

Paper IV (The teriparatide study): Reg. No. 2004: M-004, approved in 2004, Reg. No. 2006: 098, approved in 2006, and Reg. No. 1142-18/2019-00738, approved in 2019, Reg. No. 386-92, approved in 1993, Reg. No. 543-00, approved in 2001, and Reg. No. 2019-05675, approved in 2020.

RESULTS

Paper I + II

Prevalence of HPT and nHPT

The findings in both studies, I and II, were that calcium aberrations, vitamin D insufficiency and elevated PTH were common in the population.

In Paper I, of the 608 men and women, age range 25-64 years, 4% had HPT at baseline, irrespective of S-Ca, of whom 2% had nHPT. At the follow-up 13 years later, the prevalence of nHPT in the entire group had increased to 11%. Among subjects with nHPT at baseline, three had persistent nHPT, three had normalized S-PTH, one had normal S-PTH but elevated S-Ca, two were lost to follow-up and three were deceased. Nine subjects (1.5%) had pHPT at baseline. One of them was lost to follow-up but none of the remaining eight or those with nHPT was operated on for pHPT during the follow-up period. The cohort was followed until 2022, *i.e.,* 27 years later, (unpublished data). None of the individuals with nHPT developed pHPT or were neck-operated (Table 5).

Table 5. Examination of subjects with normocalcemic vitamin D sufficient hyperparathyroidism (nHPT), 27 and 14 years after the diagnosis in 1995 and 2008, respectively, at the age of 25-64 years, for neck operation, primary hyperparathyroidism, fractures, and mortality.

nHPT	**1995–2022 n = 12**	**2008–2022 n = 45**
Lost to follow-up n (%)	2 (17%)	8 (18%)
Neck operation n (%)	0 (0%)	0 (0%)
Primary hyperparathyroidism n (%)	0 (0%)	0 (0%)
Fractures during follow-up n (%)	1 (10%)	11 (30%)
No events, alive n (%)	4 (33%)	18 (40%)
Deceased n (%)	5 (50%)	8 (22%)

A similar prevalence of nHPT, 2.8%, but higher HPT in general (9.3%) was found at baseline among 750 men at the age of 50 years in Paper II, in comparison with the WHO MONICA population in Paper I.

According to laboratory findings, three men had asymptomatic pHPT but none of them was neck-operated when medical data were re-evaluated 21 years later.

Vitamin D insufficiency (S-25(OH)D < 50 nmol/L) defined according to the IOM (13) was found in 32% at the re-examination of 410 men and women in Paper I, and in 55% of men at baseline in the "Study of Men Born in 1943", Paper II.

Comorbidity and mortality

In Paper I, subjects with nHPT had a higher prevalence of hypertension at follow-up, in comparison with those with normal S-PTH. The S-PTH levels were positively correlated with age and BMI but none of the comorbidities turned to significant after adjusting for those variables. No differences in factors that influence cardiovascular disease and mortality were found between the groups with and without HPT (blood glucose, insulin, or lipids). In the same population, kidney stones, fractures, myocardial infarction ($p = 0.16$) and stroke ($p = 0.56$) did not differ between subjects with nHPT and those with normal S-PTH level after 13 years. No difference in fractures, cardiovascular diseases or mortality was seen between groups after 17 years.

In Paper II, the outcomes after 21 years were compared between men with elevated S-PTH of any cause (HPT), irrespective of S-Ca, and those with normal S-PTH at baseline. No association between the S-PTH level and morbidity or mortality was found in a univariate analysis during the 21 years of follow-up. No statistically significant differences between groups with and without HPT were observed in fractures HR 0.92 (95% CI 0.33-2.15), cancer HR 0.83 (95% CI 0.47-1.46), myocardial infarction HR 1.40 (95% CI 0.92-2.15), stroke HR 1.26 (95% CI 0.31-5.17), or mortality HR 0.83 (95% CI 0.47-1.46) at follow-up, irrespective of the observation that more men were both previous and daily smokers in the group with normal S-PTH.

Interestingly, a cut-off level of S-25(OH)D $\geq$ 90 nmol/L in Paper I and a cut-off level of S-25(OH)D $\geq$ 100 nmol/L in Paper II resulted in normal S-PTH in all individuals from the examined populations (Figure 12 a, b).

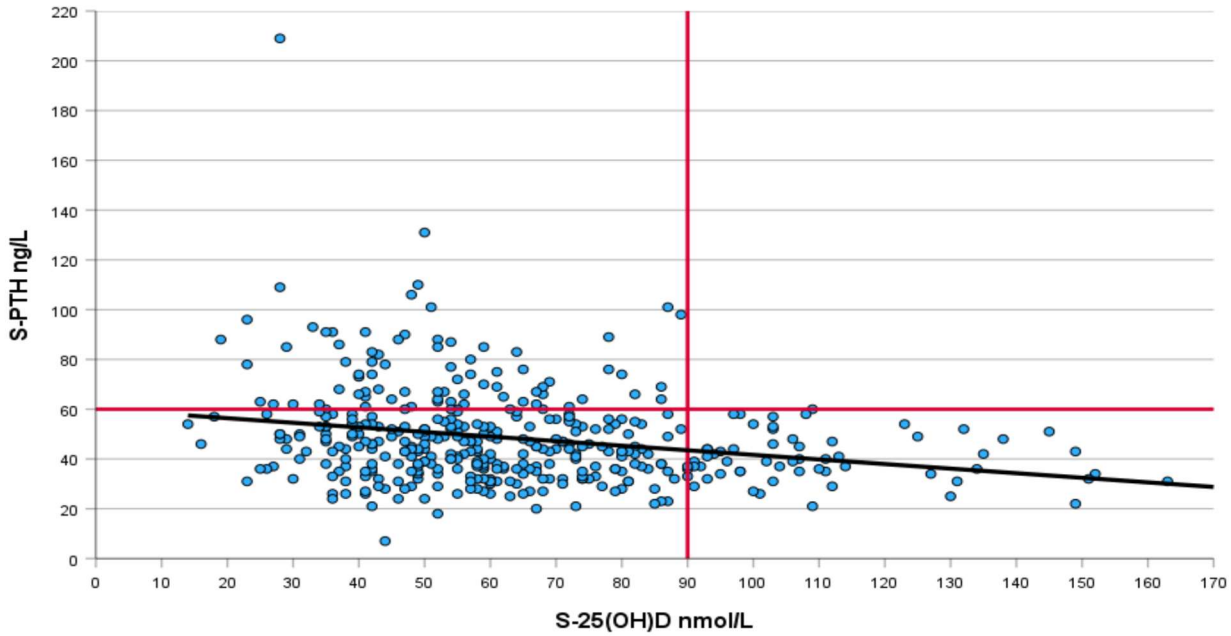


Figure 12a. Simple linear regression between S-PTH and S-25(OH)D in men and women, n = 410, in Paper I. The red line is drawn at 90 nmol/L for S-25(OH)D and at the upper reference level of 60 ng/L for S-PTH. S-PTH: serum parathyroid hormone; S-25(OH)D: serum 25-hydroxy-vitamin D.

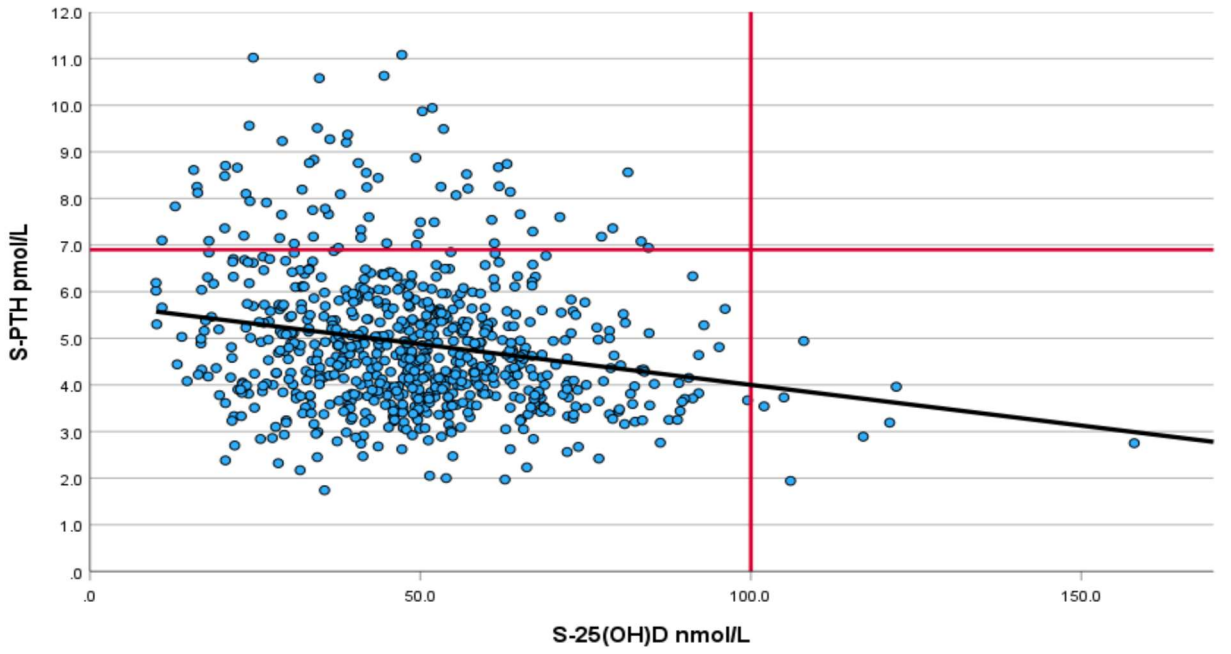


Figure 12b. Simple linear regression between S-PTH and S-25(OH)D in men, n = 750, in Paper II. The red line is drawn at 100 nmol/L for S-25(OH)D and at the upper reference level of 6.9 pmol/L for S-PTH. S-PTH: serum parathyroid hormone; S-25(OH)D: serum 25-hydroxy-vitamin D.

Paper III

Prevalence of HypoPT

HypoPT was mainly iatrogenic, and women were more affected by the disease, with a mean age of 58 years. The prevalence in the studied population was 20.5/100,000 inhabitants. HypoPT was a postoperative complication in 80% of the patients. Of all performed surgeries, 77% were due to benign causes such as thyroidectomy after Graves' disease or multinodular non-toxic goiter. Among patients with HypoPT, 74% had hypocalcemia and needed treatment with calcium substitution at different doses and/or active vitamin D.

HRQoL, comorbidity and mortality

The self-reported quality of life in HypoPT was markedly lower in comparison with the general population, based on the HRQoL questionnaires SF-36 and EQ5D-VAS. In the physical component of the SF-36, patients with HypoPT scored 40.0 (IQR: 21) compared with 51.2 (IQR: 14.6) in the general population ($p < 0.001$), and in the mental component, patients with HypoPT scored 43.1 (IQR: 17.4) vs. 56.1 (IQR: 13.3) ($p < 0.001$) in controls. Patients with postoperative and non-postoperative HypoPT presented no significant differences in the HRQoL questionnaires. The physical summary component differences between the groups of postoperative vs. non-postoperative HypoPT resulted in a p value of 0.332, and the mental summary component in a p value of 0.571. The EQ5D-VAS presented similar results; 68.55 (IQR: 35) vs. 70 (IQR: 32) and $p = 0.308$, respectively, in the groups of postoperative and non-postoperative HypoPT.

Patients with non-postoperative HypoPT ($n = 40$) were younger, used less medication and less calcium substitution. No differences between postoperative and non-postoperative patients were seen in their anthropometric and biochemical measurements, comorbidity, and mortality.

As expected, patients with HypoPT had lower S-Ca, S-PTH and also lower S-TSH compared with the general population. The documented nefrocalcinosis was rare in patients with HypoPT (one patient). According to the medical records, 2% had renal insufficiency. Fewer fractures but similar mortality was found in patients with HypoPT compared with the population sample.

Paper IV

Compliance, side effects and mortality

Forty women with severe osteoporosis and a mean age of 69±11 years were included in the teriparatide study. Fractures and BMD measured with DXA were followed up to ten years. Five patients did not complete the treatment because of treatment-related side effects such as fatigue, dizziness, and pain in the limbs. One patient suffered from a myocardial infarction and died before completing the treatment. After completing the treatment, 13 patients died before reaching ten years of follow-up and one was unable to participate in the reexamination. Twenty women (50%) completed the ten-year follow-up period from treatment start.

Patients with osteoporosis who participated in the teriparatide study had lower HRQoL measured with VAS compared with the WHO MONICA population (median 51 mm vs. 80 mm, $p < 0.001$). HRQoL did not improve after completing the treatment with teriparatide ($p = 0.78$) or ten years after treatment start ($p = 0.69$). The results were similar for the VAS and in the five HRQoL domains of the questionnaire during the ten-year follow-up in women with severe osteoporosis.

The EQ5D-VAS for subjects in the different study groups in Paper I, III and IV, respectively, are shown in Figure 13.

Fractures and BMD

The main inclusion criterion to participate in the teriparatide treatment study was severe osteoporosis with at least one vertebral compression and, as a result, all patients had at least one fracture at baseline. At the ten-year follow-up, the fracture rate in the teriparatide-treated women had declined from 100% to 35% ($p < 0.0001$) and was comparable with the WHO MONICA population, 28% after ten years.

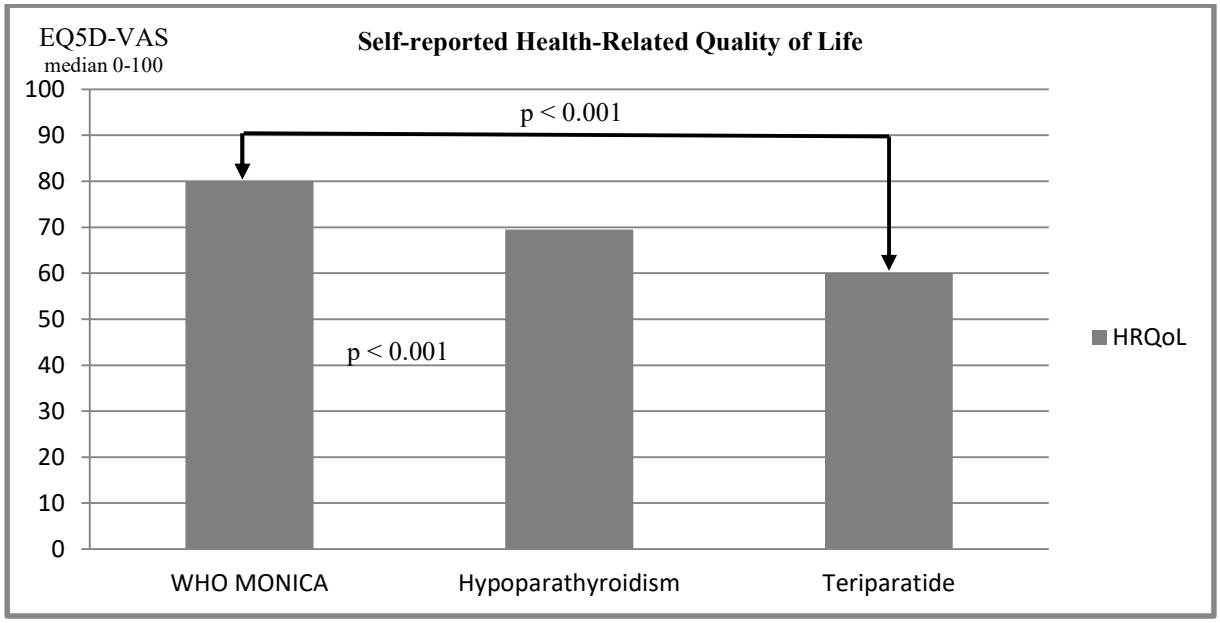


Figure 13. Self-reported Health-Related Quality of Life (HRQoL) for patients with hypoparathyroidism in Paper III, for patients treated with teriparatide after completing their treatment in Paper IV and for the population sample from the WHO MONICA study, Gothenburg Sweden. The EuroQoL-5 Dimensions Visual Analogue Scale (EQ5D-VAS) with a median score of 0-100 mm was used.

The fracture prevalence in the population did not change significantly during follow-up, with 25% at baseline to 28% after ten years.

Fractures in all the studied groups in this thesis (Papers I, II, III and IV) are shown in Figure 14.

Fracture results in the teriparatide group in Paper IV were also compared with the placebo group from the GH study (78). Fractures did not decline in the placebo group during the follow-up compared with baseline.

Of the women who completed the teriparatide treatment and deceased, five had new fractures during the follow-up. All suffered from a hip fracture, and one also had an upper arm and a rib fracture. The period from treatment start to the fractures varied from 1.5 to 9 years. Patients passed away one to two years after their hip fracture.

Bone measurement with DXA in the femoral neck and lumbar spine and comparison of BMD at baseline, 1.5 and ten years later was used to evaluate the effect of the teriparatide treatment. The same method was used to measure changes in the femoral neck and lumbar spine in the placebo-treated patients from the GH study.

A significant increase in femoral neck BMD ($p = 0.03$) and in lumbar spine BMD ($p < 0.001$) was seen in the teriparatide treated group after 1.5 years. At the same follow-up time, placebo-treated patients had an unaltered femoral neck BMD ($p = 0.13$) but increased BMD in the lumbar spine compared with baseline ($p < 0.001$). There were no statistically significant changes in BMD compared with baseline levels in either region of interest at the ten-year follow-up in either the teriparatide or the placebo-treated group.

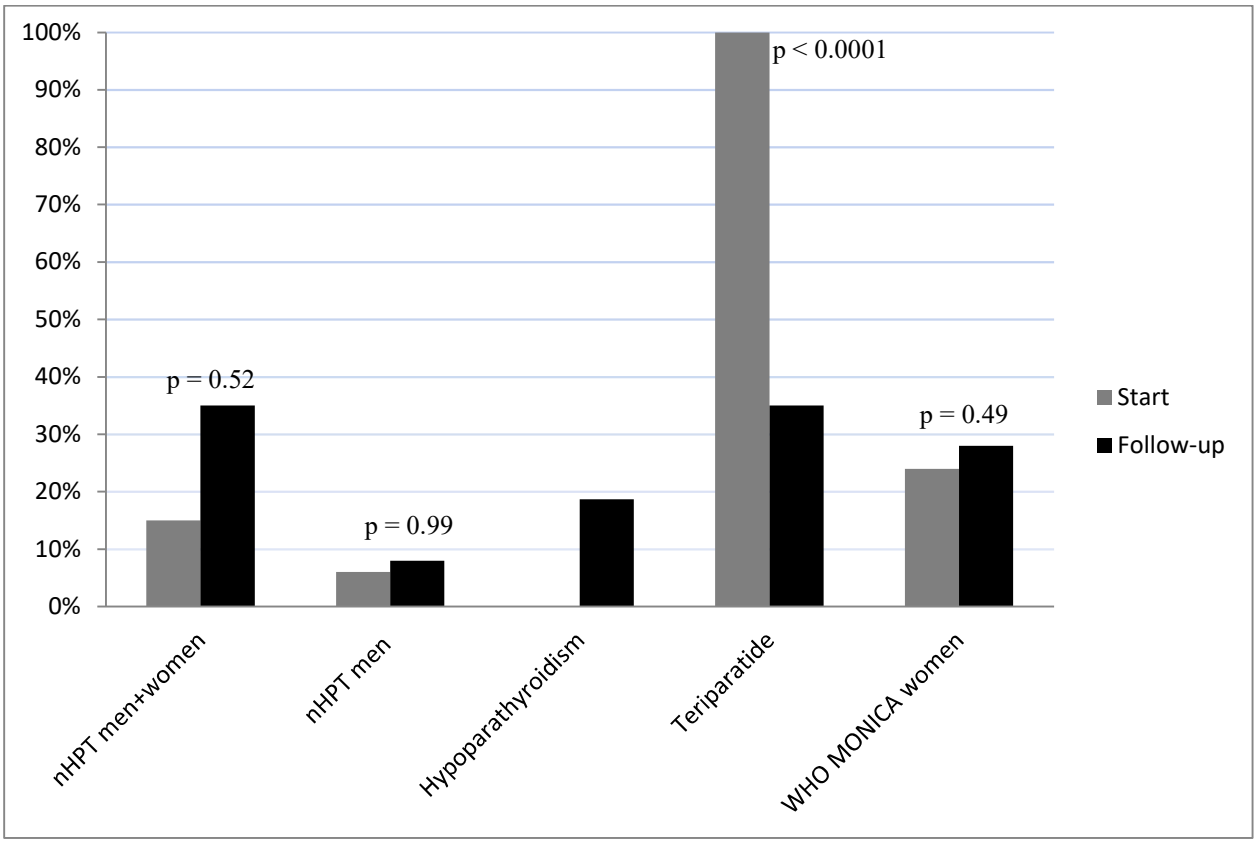


Figure 14. Percentage of fractures in all study groups: men and women with normocalcemic vitamin D sufficient hyperparathyroidism (nHPT) at start and follow-up from Paper I, men with nHPT at the age of 50 and 21 years later from Paper II, patients with hypoparathyroidism from Paper III, at treatment start and ten years later for patients with osteoporosis treated with teriparatide from Paper IV and age-matched women from the WHO MONICA population in Paper IV during the same period as the teriparatide treatment. P levels indicate a comparison between start and follow-up within groups.

DISCUSSION

Hyperparathyroidism clinical implications

The definition of HPT and especially nHPT is a hot topic and still debated by experts on parathyroid disorders (81). This leads to different inclusion criteria in studies. This, in turn, makes it difficult to compare HPT and nHPT when estimating the real prevalence of the disorders, predict the natural history and form evidence-based guidelines for the management and treatment of HPT. The data are even more confusing for nHPT.

The Fourth International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism proposed that high S-PTH and normal S-Ca ion and/or albumin-adjusted S-Ca on at least at three different occasions within a time interval of 3-6 months, in vitamin D-sufficient subjects [S-25(OH)D > 50 - 75 nmol/L] was needed for the diagnosis of nHPT. All other causes of secondary elevation of S-PTH had to be excluded before that (82).

The European expert group PARAT recently proposed an algorithm to minimize the risk of misclassification and confirm the diagnosis of nHPT (15). The Fifth International Workshop in 2022 divided pHPT based on the cause of the investigation into symptomatic pHPT and asymptomatic pHPT and nHPT based on findings in target organs in those with or without bone or kidney complications (39) (Figure 15).

The estimated prevalence of nHPT in the WHO MONICA population in Paper I was higher than described in some previous studies (8, 83), lower than a Spanish and a Brazilian study (84, 85), and similar to other population-based studies (86, 87). Misclassification due to selection bias, different cut-off levels of S-25(OH)D, age, obesity, and the number of participants seem to be the main reasons for the differences observed between the findings from those studies.

Elevated S-Ca levels were used to identify postmenopausal women with HPT in the study by Lundgren et al. (8) and, as a result, subjects with normal S-Ca were excluded from baseline, thereby underestimating the number of nHPT patients in the secondary analysis. The definition of nHPT was based solely on S-PTH and repeated S-Ca levels but did not include S-25(OH)D, which also affected the number of subjects with nHPT and the estimated prevalence (8).

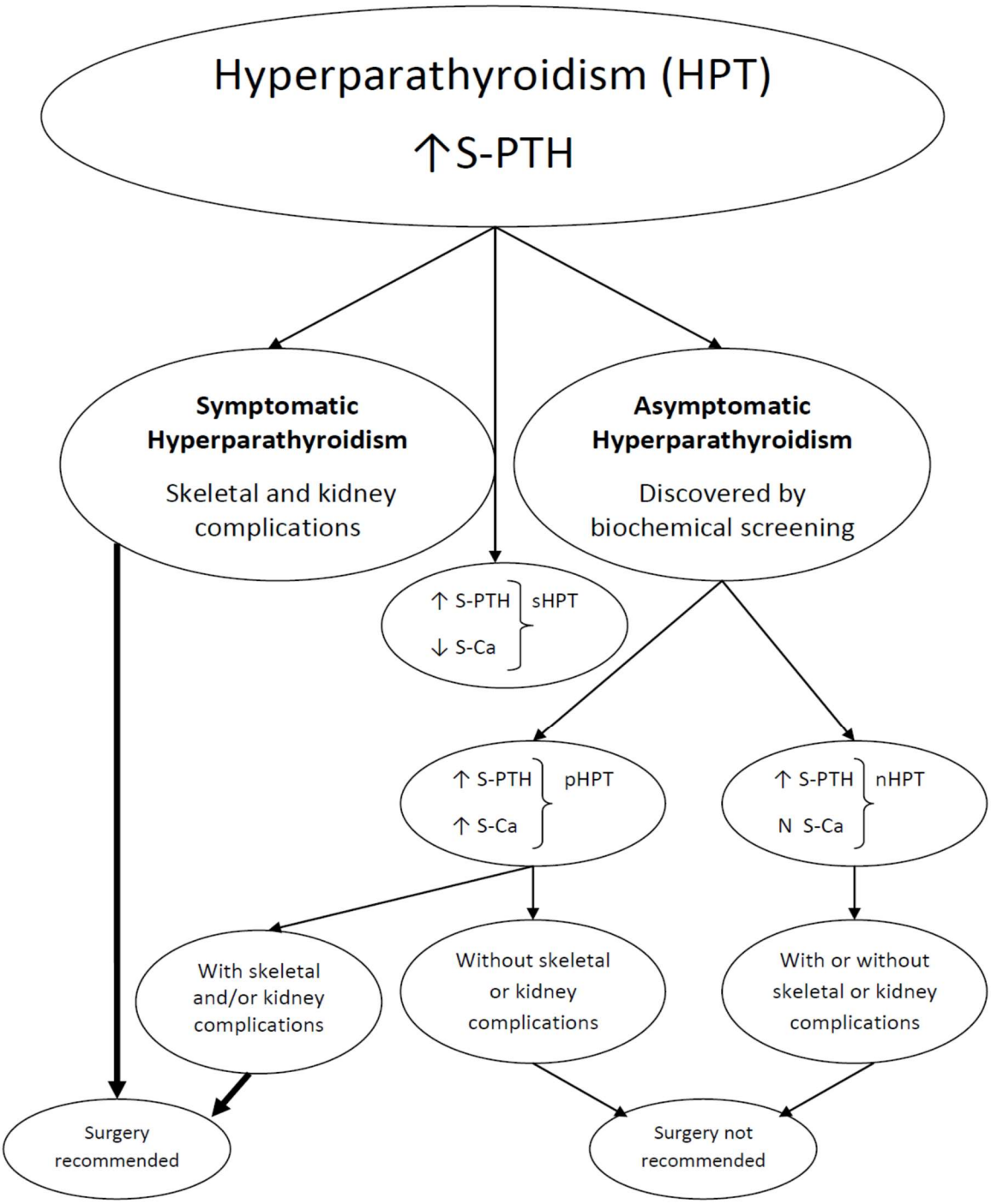


Figure 15. Definitions, main clinical manifestations, and treatment recommendations in hyperparathyroidism (HPT), according to the 5th International Workshop (39). Modified drawing by the author. Serum Parathyroid hormone (S-PTH); Serum calcium (S-Ca); secondary hyperparathyroidism (sHPT); primary hyperparathyroidism (pHPT); normocalcemic vitamin D sufficient hyperparathyroidism (nHPT); N: normal levels; ↓: low levels; ↑: high levels.

In the study by Vignali et al., the study population was younger than the WHO MONICA population and the level for vitamin D sufficiency of S-25(OH)D was set to 75 nmol/L compared with 50 nmol/L, the cut-off level in Paper I, proposed by the IOM (13, 83). When the S-25(OH)D level was ≥ 90 nmol/L in Paper I, the prevalence of nHPT was 0% (Figure 12a). In Paper II, none had S-PTH above the reference level when S-25(OH)D exceeded 100 nmol/L (Figure 12b). It is described in population studies that S-PTH increases with age, independent of other factors influencing S-PTH levels (88, 89). The younger age in combination with the higher cut-off levels of S-25(OH)D resulted in fewer subjects with nHPT in the study by Vignali et al. in comparison with Paper I. Hence, nHPT seems to be secondary to vitamin D-insufficient levels but before hypocalcemia has developed in some cases.

In the study by Marques et al. from a referral bone center, postmenopausal women with osteoporosis and a high frequency of kidney stones (29%) and fractures (21%) and a cut-off level of < 40 ml/min, to exclude subjects with kidney impairment as indicated by eGFR, showed a 9% prevalence of nHPT (85). A selection bias with subjects having clinical manifestations in target organs and inclusion of subjects with low eGFR in that study is probably the explanation for the overestimated prevalence of nHPT in comparison with randomly selected populations without specific symptoms and normal kidney function from Papers I and II. In a population-based study from Spain, the prevalence of nHPT was calculated from 100 women to 6% at baseline as well as after one year (84). The high BMI at baseline and after one year (30.5±5.8 kg/m² and 31.2±5.9 kg/m², respectively) may explain the high prevalence of nHPT as obesity was associated with higher S-PTH (88, 90). The number of participants in the study and the limited statistical power may also have influenced the results.

The results at baseline in Paper I are in line with two other population-based studies, the Dallas Heart Study and the Canadian Multicenter Osteoporosis Study with a prevalence of 3.1% and 1.7%, respectively (86, 87). The similarities are probably due to the lack of referral bias in those population-based cohorts, the examination of both men and women of approximately the same age and the same criteria to define nHPT.

At the re-examination in Paper I, 13 years later, nHPT was found in 11% of the population studied. The finding can be due to the ageing of the cohort, as the S-

PTH levels increase with age independent of S-25(OH)D levels or kidney function, according to population studies from Sweden and Australia (88, 89).

In the study of men born in 1943 in Paper II, the prevalence of HPT was 9.3% at the age of 50 years, 2.8% of the nHPT and 0.4% of the pHPT patients. To my knowledge, there is only one previous study that has estimated the prevalence of nHPT in men to 0.4%, which is lower than our findings (86). However, the prevalence of nHPT in Paper II was similar to other community-based samples of men and women in Paper I, the Canadian Multicenter Osteoporosis Study, and the Dallas Heart Study (86, 87). HPT in general was also higher in men in Paper II than in the Osteoporotic Fracture in Men study (9.3% vs. 3.7%), but pHPT was lower in men in Paper II than in the Osteoporotic Fracture in Men study (0.4% vs. 0.7%) (86). The difference in the size of the study populations probably influenced the estimated prevalence of different types of HPT.

There are differences between subjects with nHPT discovered secondary to target organ symptoms and referred to specialist bone units, and subjects without classical symptoms. This could be recognized in the latest guidelines, which divided nHPT based on those criteria but considered that there is insufficient evidence to recommend PTX for either of those groups with nHPT (39). Asymptomatic individuals with nHPT from the general population, accidentally diagnosed and apparently without any secondary organ affection, seem to undergo another natural development compared with subjects referred to bone units. Based mainly on referral population studies, nHPT was considered the early stage of pHPT (36). In a study by Lowe and colleagues, 19% of patients with nHPT, referred to a bone metabolic center for a bone disease, kidney stones or accidentally found nHPT, developed hypercalcemia within three years of the nHPT diagnosis (91). Siprova et al. identified 187 patients with nHPT and after a follow-up period of six years, 19% became hypercalcemic, most of them (67%) during the first two years (92). In the study by Garcia et al. with a population-based cohort, none of the six subjects with nHPT developed hypercalcemia (84). In the Dallas Heart Study, a population-based screening study, only one subject of n = 108 with nHPT developed pHPT after eight years of follow-up (86). In Paper I, after 13 years, only one subject developed hypercalcemia with normal S-PTH. At a follow-up analysis in 2022 (data not published), none of the n = 45 subjects having nHPT in the reexamination in 2008, according to their medical records, was neck-operated, which can be interpreted as nobody developing symptomatic pHPT (Table 5).

There was no difference in the prevalence of fractures between subjects with nHPT and those with normal S-PTH and no increase in kidney stones was observed in Paper I and Paper II at follow-up compared with subjects from the same population and with normal S-PTH. In a randomly selected population study, Palermo et al. used the definition from the Fourth International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism for nHPT (37) to enroll consecutively 47 subjects with nHPT and 41 with pHPT in a prospective cross-sectional study, and compared their clinical, laboratory and radiological findings with 39 age- and sex-matched controls. It was concluded that biochemically, the nHPT patients had a phenotype between pHPT and healthy controls, but the bone characteristics of the nHPT patients were similar to that of controls (93).

According to guidelines, the grade of evidence cannot justify parathyroid surgery in HPT to improve cardiovascular and metabolic disorders (39). More studies are needed to confirm this association (37, 39). In a small case-control study it was found that strongly selected patients with nHPT and osteoporosis and/or nephrolithiasis had similar cardiometabolic disorders (hypertension, dyslipidemia, insulin resistance, diabetes mellitus, high BMI), and a similar risk of cardiovascular disease as patients with pHPT (94). In patients with nHPT, the potential causes of sHPT were examined and patients with a risk of sHPT were excluded from the study. All patients had S-25(OH)D > 75 nmol/L and groups were compared with each other and with population-based controls (94). Controls with diabetes mellitus, manifest pHPT, treated hypertension and treated hyperlipidemia were excluded. According to study results, successful PTX improved all cardiometabolic disorders and decreased cardiovascular risk scores (94). A positive correlation with treated hypertension was found in Paper I but no association with an increased risk of myocardial infarction, stroke, or metabolic disorders. In Paper II, the risk of having stroke and myocardial infarction in 50-year-old men after 21 years without any specific treatment to reduce S-PTH was similar for those with HPT of any kind and those without elevated S-PTH. The same results were found when comparing subjects with nHPT with those with normal albumin-adjusted S-Ca and normal S-PTH.

The different findings regarding nHPT, comorbidity and outcome probably depend on the presence or not of manifestations from the skeleton and/or the kidneys and different clinical phenotypes of apparently the same biochemical disorder. This may lead to the conclusion that accidentally discovered nHPT in a

non-referral population seems to have a benign course and, as a result, PTX should not be recommended in those subjects with nHPT. At the same time, a considerable part of subjects with nHPT and manifestations from the skeleton and/or the kidneys may need another follow-up frequency and treatment approach where PTX is considered as an option.

Parathyroidectomy (PTX) indications and complications

PTX is recommended as the only curative treatment for symptomatic pHPT (39). However, PTX in mild/asymptomatic forms is not always the only treatment option. In a recently published Scandinavian study it was concluded that patients with mild pHPT did not have higher morbidity or mortality than patients who had undergone PTX (95). Patients operated on in high volume centers by experienced surgeons, with preoperative identification of the abnormal gland and minimally invasive surgical methods, have a low risk of developing postoperative complications. One of the complications after PTX is HypoPT. In most cases, this complication is limited to a short period of time after the operation. However, in rare cases HypoPT develops into a chronic irreversible disorder with variable grade of PTH insufficiency or a total lack of the hormone. The risk of devascularization or injury of the parathyroid glands increases with the number of parathyroid glands that are removed (96). In case of a new PTX with a total thyroidectomy or extended front neck surgery, for example secondary to thyroid cancer, the risk of HypoPT is high (96).

Hypoparathyroidism (HypoPT) causes and treatment

The prevalence of HypoPT varies between studies and countries. This is due to the different incidence of HypoPT secondary to the number of neck operations, as 75% of HypoPT is postoperative and only 25% is due to other causes (97). The incidence of postoperative HypoPT varies depending on local traditions in the indication of neck operations. The differences are mainly due to benign disorders such as Graves' disease and non-toxic goiter where other treatment options may be considered. An experienced surgeon can also contribute to minimize the risk of postoperative HypoPT and other complications. The use of the latest imaging techniques to localize the hypertrophic parathyroid gland preoperatively and procedures such as minimally invasive operations and

intraoperative measuring of S-PTH reduce the risk of devascularization or injury to the parathyroid glands. This could allow for successful removement of the pathological gland. According to studies, the more parathyroid glands in situ, the smaller the risk of developing postoperative HypoPT. The reimplantation of a parathyroid gland must be limited to only accidentally removed glands (96).

If extended front neck surgery is inevitable, such as in thyroid or parathyroid cancer, and chronic postoperative HypoPT results, the treatment target is to maintain S-Ca or S-Ca ion levels at low normal levels or just below the lower calcium reference interval, phosphate at high normal levels, and the patient free from symptoms (16, 21). Traditionally, calcium and active vitamin D supplements are used to maintain stable S-Ca levels and to treat symptoms but not as PTH substitution therapy. The phosphaturic effect of PTH in the kidneys is not replaced and, as a result, phosphate is not properly eliminated. High phosphate levels seem to predispose to soft tissue calcification and calcification in the basal ganglia of the brain, cataract, kidney stones, kidney impairment and unphysiological calcification in other organs (Figure 6).

Another function of PTH in the kidneys, which classic treatment cannot replace, is the reabsorption of calcium, which in some patients with HypoPT and hypercalciuria is partially compensated for with the use of thiazides. The effect of PTH in bone remodeling is another issue that conventional treatment with calcium/vitamin D cannot imitate. Bone in patients with HypoPT is highly mineralized and BMD measurements performed with DXA are above normal compared with the population, but biopsies and new radiological techniques in some studies question the quality of the bone (98, 99). The possibly reduced quality of the bone may predispose to fractures. However, in Paper III, fractures were significantly fewer in patients with HypoPT compared with the background population. In registry studies from Denmark, fractures were not more frequent in patients with HypoPT than in the population, which is in line with our findings (20, 44). These results may be due to the undertreatment of osteoporosis in the population (58) and/or to the protective effect of calcium/vitamin D on the mineralization of bone in patients with HypoPT. During recent years, cholecalciferol was also added to the conventional calcium/active vitamin D therapy in subjects with HypoPT and osteoporosis with fractures in Paper III, which may have contributed to fracture prevention. The regular examinations of the subjects with HypoPT at a specialist endocrine

clinic and fall prevention advice may also have played a role for the lower fracture prevalence.

The only PTH-dependent mechanism that conventional treatment of HypoPT seems to replace is the absorption of calcium from the bowel, by administering oral calcium and active vitamin D supplements, often in high doses. If patients suffer from a malabsorptive condition, management of the disease is challenging due to the low uptake of calcium from the bowel. Subjects treated for obesity by bariatric surgery, which is increasing in number, are at an increased risk of malabsorption. The higher risk of developing hypocalcemia after thyroidectomy in patients with previous bariatric surgery was presented in a recent survey (100). The main mechanisms creating difficulties in the management of those patients were the reduced stomach acidity and the bypassing of the duodenum and proximal jejunum, which are the parts of the gastrointestinal tract with the higher absorption of calcium that contribute to malabsorption (100). In Paper III, five patients had gastric bypass surgery in their medical history. They were without any other signs of malabsorption disorders or vitamin deficiencies and reported very low HRQoL scores due to symptomatic fluctuations of S-Ca levels in line with the findings from the above-mentioned study (100). In these cases, the multiple mechanisms that PTH mediates to maintain calcium balance in the blood cannot be replaced by traditional management of HypoPT. This leads to calcium fluctuations in the circulation. As a result, S-Ca can be elevated, but more often decreased and therefore lead primarily to hypocalcemic symptoms in the patients. Those symptoms in combination with the daily need for extensive medication influence patient wellbeing.

In Paper III, patients with HypoPT, independent of the cause, scored lower compared with the population on both the mental and physical HRQoL domains. Similar findings were found in a previous controlled study in Norway (19).

PTH 1-84 was introduced as a treatment option for HypoPT, leading to an increased interest among clinicians managing patients with HypoPT to prescribe the new drug, which replaces the missing hormone. The high treatment costs and the lack of official guidelines have made the prescription of PTH 1-84 problematic. National reimbursement systems are based on different principles and healthcare authorities need to estimate the cost and the cost-effectiveness of the new recommended treatment. Experts recommend first-line treatment with conventional calcium/vitamin D in patients with many symptoms and difficulties in successfully managing the disease (15, 101). To identify those

patients, more tools than laboratory findings, which document only a part of the problem, are needed; for example HRQoL questionnaires. In Paper III, by using scores from two generic HRQoL questionnaires, the EQ5D-VAS and the SF-36, in combination with laboratory findings, patients with any cause of HypoPT were classified in different groups. The "patient presentation matrix" (Figure 7) principle was used, and patients were divided into four categories to estimate the number of patients in need of PTH 1-84 (45). Patients with a high level of wellbeing were divided into those who fulfilled the target levels of S-Ca according to the guidelines, and those with hypocalcemia. The same division principle was used for patients with a low level of wellbeing. According to this classification, approximately 23% of the patients included in study III in this thesis would potentially be eligible for PTH 1-84 treatment, *i.e.,* patients with poor wellbeing together with low S-Ca.

The administration of PTH in patients with HypoPT seems to be the most physiological treatment approach. In all other endocrine disorders, the treatment of choice is always to administer the hormone that is deficient or missing. Unfortunately, the high cost of lifelong treatment with PTH and the by far cheaper conventional treatment with calcium and active vitamin D is a major problem. Another problem is the rarity of the disease, *i.e.,* the small number of patients, which makes it difficult to have good knowledge of the multiple organ affections in HypoPT. It is not clear if the disorders that develop are caused by the disease itself or by the treatment or both. The limited knowledge cannot offer good and/or enough arguments on the cost-effectiveness of the new expensive drug. To overcome the problem of the limited number of patients, well-planned international multicenter studies must be performed to reach firm conclusions with high external and internal validity. As the major cause of the disorder remains the postoperative HypoPT, the prevention of this complication is very important. High volume centers and experienced surgeons need to perform front neck operations. National coordination of this type of surgery is warranted to reach that target.

The recently approved adjuvant treatment with PTH 1-84 has been shown to produce controversial effects on HRQoL in different studies (102-105). In addition, technical problems developed, and the drug was withdrawn from the United States in September 2019, but it is still available in Europe for those already using the treatment. Another PTH analog, TransCon PTH, which is a long-acting PTH 1-34 showed promising results in recently published clinical

trials by maintaining S-Ca, serum phosphate and normal calciuria with once daily administration and improving HRQoL from baseline (68).

Osteoporosis, teriparatide and HRQoL

Another form of the same molecule PTH 1-34, teriparatide, is available for the treatment of severe osteoporosis. Teriparatide is the only anabolic agent approved for osteoporosis that uses a fragment of the body's own hormone in intermittent administration to promote bone formation. Since the introduction of the treatment in Europe in 2003, many studies have shown a beneficial effect on bone and HRQoL in patients. However, the long-term effects on bone, fractures and HRQoL in comparison with the population is unknown. In Paper IV, data were presented on a ten-year follow-up of postmenopausal women with severe osteoporosis and at least one vertebral fracture who were treated for a median of 14 months with teriparatide. The 40 women were examined clinically once a year and their results were compared with age-matched women from the general population examined within the framework of the WHO MONICA study and placebo-treated patients from another study of women with osteoporosis from the same city (74). Of the 40 women, 50% participated in the examination ten years after treatment start and completed the DXA examination. A statistically important improvement of the same magnitude as the pivotal original study from Neer et al. was observed at both the femur and the lumbar spine after 18 months from the start of treatment with teriparatide (54). The result was also significantly different from what was seen in the placebo-treated patients. After ten years, the difference from placebo was not significant, and BMD returned to baseline levels. The number of fractures decreased since the treatment start when all had at least one vertebral fracture. Fractures in the teriparatide-treated group were at the same levels at follow-up as in women in the general population who were followed in parallel. This reduction in fracture prevalence from 100% to 35% in the teriparatide-treated group might be explained by other, additional bone-specific treatment and repeated fall prevention advice by the physician at the annual visits. The combined effects of teriparatide and the transient BMD increase during treatment, followed by an antiresorptive agent and lifestyle advice, indicate a positive effect of teriparatide. On the other hand, it is known that osteoporosis in the population is undertreated and probably the reason for the relatively large number of fractures in the population (28%). The return of BMD to baseline levels in the teriparatide group after ten years

demonstrates that antiresorptive treatment after teriparatide is necessary to preserve the increased BMD after the anabolic treatment. One could speculate that if teriparatide could be administered for a longer period without safety restrictions, the effect on the skeleton would be more pronounced and long-lasting.

HRQoL in Paper IV did not improve to the same extent as in other shorter studies after 18 months of teriparatide from treatment start (60, 64), nor was HRQoL improved after ten years in the present study (IV). The main reason seems to be the presence of vertebral fractures in the studied population, which probably affects HRQoL, both with pain and disability, more than other types of fracture.

Fragility fractures generally influence the level of HRQoL negatively (61-63, 106). Those findings confirm that the best treatment for maintaining a good quality of life is prevention of the first fracture. By identifying patients with a fall risk in need of treatment for osteoporosis and by offering early treatment, the benefits for both patients and society are huge. Treatment with an anabolic agent (for example teriparatide) is a reasonable treatment choice. Unfortunately, the treatment costs are still considerably higher than treatment with an antiresorptive agent. However, this treatment approach would be cost-effective with time, considering the limitations of bisphosphonates and the risk of a devastating or even life-threatening fracture.

Strengths and Limitations

The main strength of Paper I is the randomly selected population, which offered the possibility to study a group without selection bias during a long period of time, with two measuring points of laboratory variables 13 years apart. The association of the information provided by blood samples, physical examination, medical records, medication, and nationally covering registries, such as the death register, offered the possibility to follow the development of nHPT and HPT up to 17 years. The same conditions were available for Paper II, where the follow-up time was up to 21 years. In Paper II, a relatively large and homogenous random population sample of men only, of the same age and from the same city, was studied. This offered the opportunity to investigate the comorbidity and mortality for an endocrine disorder, HPT, and its more recently

described phenotype nHPT that is often studied in women or, ideally, in a mixed population of men and women.

In Paper III, a large cohort of patients with a rare disease, HypoPT, was examined by using the medical records and the diagnosis codes in one of the largest referral hospitals in Europe, with both endocrine medical and surgical clinics, Sahlgrenska University Hospital, Gothenburg, Sweden. A cohort of a similar size was presented in a recent study from Canada using the whole country's national register of HypoPT (97).

In Paper IV, the uniquely long follow-up time of ten years in real-life conditions by the same investigator and with the first available anabolic treatment for osteoporosis is a major strength. The registration of laboratory findings, medication, DXA, fractures and HRQoL during all those years offers valuable information in clinical medical practice.

The disorders examined were compared with the background population in all four papers, which is a major strength regarding the validity of the results from the studies. In Paper IV, a placebo-treated group from another study of the same disease, osteoporosis, was also used for comparison with the study population.

The studies present some limitations. In Paper I and II, the diagnosis of nHPT was based on one measurement of S-Ca and S-PTH. S-Ca ion and 24-hour urine calcium measurements were not available. The cut-off level of S-25(OH)D of >75 nmol/L to confirm nHPT in the diagnosis algorithm was not proposed as a diagnostic condition at that time. This may have led to misclassification of conditions such as nHPT. Our findings are similar to those of other population studies both regarding prevalence and disease development, which speaks against a high grade of misclassification.

In Paper III, the laboratory results, mainly S-Ca and S-Ca ion, used to classify the patients with HypoPT into different groups, were not analyzed at the same time as the patients completed the HRQoL questionnaires. There is always a risk of acute deterioration of a condition and the latest results do not always represent the steady state expected. This may underestimate the number of patients who have low well-being and low S-Ca or S-Ca ion levels and the number of patients estimated to need another treatment than conventional therapy.

In all papers, the classification of kidney function and the comparisons between groups were made with S-creatinine, which is influenced by other conditions such as muscle volume, exercise and dehydration that may have underestimated or overestimated the influence of renal function in the studied disorders.

In Paper IV, the small number of participants from only one center is a limitation that results in low statistical power. However, the long follow-up time is unique, as are the control groups from the general population and the placebo-treated women with osteoporosis.

CONCLUSIONS

The new described clinical phenotype nHPT in randomly selected individuals from the population has a relative high prevalence, 2% at baseline and 11% at follow-up after 13 years. The definition of nHPT has changed from when it was first described in 2008 and has become a diagnosis of exclusion. This will probably lead to a lower prevalence of nHPT if vitamin D levels are optimized by supplementation according to the latest guidelines (39). It seems that nHPT does not cause more fractures, higher other morbidity or mortality compared with the population after up to 27 years of follow-up.

HypoPT of any cause was associated with lower HRQoL and lower fracture risk but otherwise comparable with the population regarding comorbidity and mortality. The need for treatment with recombinant PTH 1-84 was estimated to be 20% and may improve HRQoL and laboratory findings, *i.e.,* biochemical stability in patients with HypoPT (107). Unfortunately, due to problems in the stability of the drug, PTH 1-84 was recently withdrawn from the market. Other treatment options may replace PTH 1-84 as substitution therapy (69); for example, TransCon PTH, a long-acting form of PTH 1-34, which showed independence of conventional therapy and improvement of HRQoL in patients with HypoPT in a phase 3 trial.

Teriparatide had an anabolic effect on BMD during the time of treatment, but the effect had declined to initial levels ten years later. HRQoL was low and unaffected by teriparatide in these severely osteoporotic women. However, the main outcome measure, the fracture frequency, declined. Thus, the treatment could be used as first-line bone-specific therapy in susceptible individuals. Teriparatide seems to be safe, and the treatment followed by antiresorptive therapy and fall prevention advice should not be neglected in order to assure a long-time fracture-free period of life.

Clinical implications

nHPT in asymptomatic individuals without target organ implications does not seem to progress to pHPT or influence comorbidity and mortality over more than 20 years of follow-up, according to the findings in this thesis. This is in line with the latest guidelines (39). Subjects can safely have their follow-up in primary care units. S-25(OH)D should be optimized by supplementation and

reference levels, and the recommended levels for S-25(OH)D and S-PTH could possibly be adjusted.

On the contrary, the follow-up and treatment of HypoPT is challenging because one in five patients does not feel well with standard treatment, according to this thesis. The patients' low HRQoL is resource-consuming and frustrating for medical practitioners. Our study describes the dimension of the problem by calculating the prevalence and its consequences and possible solutions, such as prevention strategies and new treatment options, *i.e.,* hormonal substitution with PTH.

Another contribution of this doctoral thesis to the medical society is the uniquely long time of follow-up studies of population cohorts and patients in real-world conditions of treatment in severe osteoporosis. The paper offers information about patient HRQoL after a devastating fragility fracture, such as a vertebral compression, to physicians and decision-makers. It seems that life never returns to normal after a serious osteoporotic fracture. The goal of the strategy must be to prevent fractures in the first place or, if they occur, to prevent recurrent fractures at any cost. To this end, starting with anabolic bone-specific agents followed by bone-preserving agents and fall prevention would be the optimal way to treat manifest osteoporosis.

Future perspectives

nHPT is a diagnosis of exclusion. If the patient is asymptomatic, the natural history does not seem to have any implications for higher morbidity or mortality. Larger studies with strict inclusion criteria have to be performed to confirm those findings. Take-home message is to measure S-PTH only if S-Ca is aberrant, and S-25(OH)D is sufficient.

National and international action plans to centralize neck surgery to clinics with experienced surgeons are warranted in order to reduce postoperative complications such as HypoPT. Multicenter studies of HypoPT comparing the effects of traditional treatment with PTH supplementation are desirable.

The upgrade of teriparatide, or other anabolic bone-specific agents, to first-line treatment to prevent more fragility fractures seems to be a cost-effective strategy in severe osteoporosis.

ACKNOWLEDGEMENTS

The conception and creation of this thesis are the result of hard work by many people to whom I would like to extend my gratitude:

I would like to begin by thanking my main supervisor Professor *Kerstin Landin-Wilhelmsen*, who introduced me to the world of research. I appreciate your stable guidance with clear targets from the start to the finishing line of my PhD. You have shared your deep knowledge and enthusiasm and supported me when needed.

I would also like to thank my co-supervisor *Penelope Trimpou*. Thank you for your feedback, your support and assistance.

I am also very thankful to have had *Christine Laine* as my co-supervisor. Thank you for your valuable comments during these years and for sharing your knowledge of bone metabolism.

Special thanks to my committed co-authors who invested their time and knowledge to achieve the best result for the articles, which are the basis for this thesis (in publication order): *Göran Oleröd*, *Anders Lindahl*, *Lennart Welin*, *Michael Fu*, *Per-Olof Hansson*, *Zoi Mamasoula*, and *Emily Krantz*.

The excellent help provided by *Stella Nakate* and the late *Sigrid Lindstrand* to coordinate the WHO MONICA project and to monitor the teriparatide-treated patients together with *Kristina Cid-Käll* and *Helena Wik* is gratefully acknowledged. My thanks also go to the entire staff at the Endocrine outpatient clinic. The excellent help from *Eva Hällås-Linder* and *Lasse Ellegård* with the DXA examinations interpretation and for presenting me the procedure of examination with DXA scans. *Peter Thorsson* for the recording of patients, the *Statistical Consulting Group* and *Georgios Lappas* for their help with the statistics are highly appreciated. Special thanks to *Eva Thydén* for helping me with presenting the printed version of my work in the best possible way.

My sincere thanks to the *heads* of the *Institution of Medicine and the Department of Internal Medicine and Clinical Nutrition, Sahlgrenska Academy, University of Gothenburg*; the *heads* of the *Department of Medicine SU/Sahlgrenska and Östra Hospital, Gothenburg*, and the heads of the endocrine sections, *Jerzy Kaczynski* at SU/Östra and *Lena Bokemark* at SU/Sahlgrenska, for providing excellent working conditions along this journey.

I appreciate and I am really grateful for the patience and the support from all my *colleagues* at *SU/Östra Hospital* during the time I was working with my research. I know that it was not always easy to take a period off to work on a project and without your loyal support this would not have been possible. Thank you! I am also thankful to the *colleagues* during my time at the section for *Endocrinology at SU/Sahlgrenska* where my research interest begun.

To all my *friends* for their moral support during my PhD project. Special thanks to *Dimitrios Chantzichristos* who was of great help during critical moments of my career.

To my *parents*, *Maria* and *Antonios Kontogeorgos*, who gave me the possibility to start this journey and be a MD in first place. They also gave me their unconditioned support and love during my entire life and helped me during my whole PhD journey. I would also like to thank my *sister Eleni Kontogeorgou* for her support.

My *parents-in-law Zenovia* and *Vladimir Perepelita* who provided my family with the support needed and the possibility to concentrate exclusively on my research when it was most necessary.

I would like to thank my *wife*, *Silvana*, for being there for me for more than half my life.

Last but not least, a special thanks to my *daughters*, *Maria* and *Lara*, who make me proud every day and give me the strength to continue my journey and to try to make our world a better place through my work as a doctor and researcher.

FUNDING

This thesis was supported by grants from the Gothenburg Medical Society, the Swedish Heart-Lung foundation, the Swedish state under the agreement between the Swedish government and the county councils, the ALF agreement, and the Healthcare Board, Region Västra Götaland, R&D.

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