Thesis

Hypoparathyroidism
neurological and cardiovascular manifestations

submitted by
Alexander Purkhart

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

and

Univ. FÄ Dr.med.univ. Tadeja Urbanic Purkart

Graz, date 17.02.2023

Declaration of Academic Integrity

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Graz, 17.02.2023 *Alexander Purkhart m.p.*

Acknowledgement

I would like to dedicate these few lines to the people who have always stood behind me throughout my studies and supported me along the way. In particular, I would like to thank my family and my closest friends, without whom neither my studies nor this thesis would have been possible.

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Abstract in german

Hypoparathyreoidismus ist eine seltene Erkrankung, die durch einen niedrigen Kalziumspiegel in Verbindung mit einer inadäquat niedrigen PTH-Konzentration gekennzeichnet ist. Weiters ist die Konzentration des Phosphats im Blut erhöht, während die des Vitamin D reduziert sein kann. Neben den typischen Symptomen wie Parästhesien und Muskelkrämpfen wird der Hypoparathyreoidismus mit einer Vielzahl unterschiedlicher klinischer Komplikationen wie Katarakt, Niereninsuffizienz, Herz-Kreislauf-Erkrankungen, Krampfanfällen, neuropsychiatrischen Störungen oder einem erhöhten Infektionsrisiko in Verbindung gebracht.

Ziel dieser Arbeit ist es, eine umfassende Zusammenfassung der vorhandenen Literatur zu kardiovaskulären und neurologischen Manifestationen des Hypoparathyreoidismus zu erstellen, um die Relevanz dieser Symptome für die tägliche klinische Praxis zu ermitteln.

Um dieses Ziel zu erreichen, wurde eine Literaturrecherche in "PubMed" durchgeführt.

Bei Patientinnen und Patienten mit Arrhythmien, verlängerten QTc-Intervallen, Anzeichen einer ischämischen Herzerkrankung oder erhöhter arterieller Steifigkeit in Kombination mit niedrigem Kalzium und/oder erhöhtem Phosphat sollte ein Zusammenhang mit Hypoparathyreoidismus in Betracht gezogen werden. Wenn ein Hypoparathyreoidismus mit diesen Komplikationen festgestellt wird, sollte eine angemessene Behandlung der endokrinologischen Erkrankung eingeleitet werden, da es sich hierbei um teils reversible Komplikationen handelt. Es erscheint plausibel, dass die Substitution mit rhPTH(1-84) ein besseres kardiovaskuläres Risikoprofil aufweist als die traditionelle Behandlung mit Kalzium- und Vitamin-D-Substitution.
Betreffend die neurologischen Komplikationen scheint die Qualität der Behandlung und damit die Dauer der Hypo-/Hyperkalzämie mit dem Ausmaß der Basalganglienverkalkung in Verbindung mit Bewegungsstörungen wie Parkinsonismus, Chorea oder Tremor zu korrelieren. Außerdem sind die Lebensqualität und die neurokognitiven Funktionen häufig beeinträchtigt.

Abstract in english

Hypoparathyroidism is a rare disease defined by low calcium levels in combination with a reduced or inadequately low PTH concentration. Furthermore, the phosphate levels might be elevated and vitamin D decreased. Besides typical symptoms such as paresthesia and muscle cramps, hypoparathyroidism has been associated with a variety of different clinical complications like renal insufficiency, cardiovascular disease, seizures, neuropsychiatric disorders, cataracts or an increased risk of infections.

The aim of this thesis is to create a comprehensive summary and analysis of the existing literature concerning the cardiovascular and neurological manifestations of hypoparathyroidism to determine the relevance of those symptoms for the daily clinical practice.

To achieve this goal, a literature search using “PubMed” was performed.

This thesis shows that when patients present with arrhythmia, elongated QTc-intervals, signs of ischemic heart disease or arterial stiffness in combination with low calcium and/or elevated phosphate, a connection to hypoparathyroidism should be considered. If hypoparathyroidism with those complications is evident an appropriate treatment should be initiated since those are partly reversible complications. For treatment it has been suggested that the substitution with rhPTH(1-84) has a better cardiovascular risk profile than traditional treatment with calcium and vitamin D substitution but existing data are scarce.
For neurological complications it seems that the quality of treatment and therefore the time in hypo-/hypercalcemia correlates with the extent of basal ganglia calcifications connected with movement disorders like parkinsonism, chorea or tremor. Furthermore, the quality of life and neurocognitive function may be impaired.

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List of Abbreviations

PTH	parathyroid hormone
QTc-interval	corrected QT-time
rhPTH	recombinant human parathyroid hormone
mRNA	messenger ribonucleic acid
ARE-BP	adenosine and uridine rich elements binding proteins
ER	endoplasmatic reticulum
Ca++	ionized calcium
CaSR	calcium sensitive receptor
1,25(OH)2D	calcitriol
GCMB	glial cell missing gene
FGF23	fibroblast growth factor 23
TGF-α	transforming growth factor α
Pi	inorganic phosphate
Ca	calcium
TRPV6	transient receptor potential vanilloid channels
GFR	glomerular filtration rate
RANK	receptor activator of nuclear factor k-B
OPG	osteoprotegerin
UV	ultraviolet
FGF-23	fibroblast growth factor-23
HR	hazard ratio
CI	confidence interval
CVD	cardiovascular disease
IHD	ischemic heart disease
VDR	vitamin D receptor
PTH-rP	parathyroid hormone related peptide
cAMP	cyclic adenosine monophosphate
CKD	chronic kidney disease
PO4	phosphate
CAN	cardiovascular autonomic neuropathy
QoL	quality of life
SF-36	RAND 36-Item Short Form
PCS	physical health evaluated by the RAND 36-Item Short Form
MCS	mental health evaluated by the RAND 36-Item Short Form
EF	ejection fraction
LVEF	left ventricular ejection fraction
HFrEF	heart failure with reduced ejection fraction
HFmrEF	heart failure with mid-range ejection fraction
HFpEF	heart failure with preserved ejection fraction
CMP	cardiomyopathy
iCa	ionized calcium
tCa	serum total calcium
BMI	body mass index
TSH	thyroid stimulating hormone
T4	thyroxine
SBP	systolic blood pressure

DBP	diastolic blood pressure
MAP	mean arterial pressure
PP	pulse pressure
cSBP	central systolic blood pressure
cDBP	central diastolic blood pressure
cPP	central pulse pressure
AP	augmentation pressure
Aix@75	augmentation index corrected depending on 75 pulse/min
PWV	pulse wave velocity
ADH	autosomal dominant hypocalcemia
Cbfa-1	Core-binding factor alpha1
hypoPT	hypoparathyroidism
ns-hypoPT	nonsurgical hypoparathyroidism
ps-hypoPT	postsurgical hypoparathyroidism
BSPDC	bilateral striopallidodentate calcinosis
IBGC	idiopathic basal ganglia calcification
BGC	basal ganglia calcification
CT	computed tomography
CSF	corticospinal fluid
Runx2	runt related factor-2
MRI	magnetic resonance imaging
FDG-PET	fluorodeoxyglucose positron emission tomography
QOL	quality of life

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1 Introduction

1.1 The parathyroid glands

The parathyroid glands are small endocrine glands that produce the parathyroid hormone (PTH) which is important for calcium regulation (1). During the embryological development normally four parathyroid glands develop. Although cases with two and up to a maximum of 12 parathyroid glands have been reported. The upper parathyroid glands are consistently located at the back of the upper thyroid lobes. In contrast the lower thyroid glands have a less consistent location. In 50 % of cases they are located in close proximity to the lower thyroid lobe. In 15 % they can be found about one centimeter beneath the lower thyroid lobe, though the location can be anywhere from the thyroid gland down to the upper mediastinum (2). The varying location of the two lower parathyroid glands can be explained by the close connection to the thymus over the course of the human embryonic development. Both evolve out of the third pharyngeal pouch and subsequently start a common decent to their final locations (3).

The parenchyma of the parathyroid glands is mostly made up of chief cells, that produce PTH. The second cell type are oxyphil cells. The function of those cells is not yet fully understood. They have a high number of mitochondria and an increased number of basophil cells. A high concentration of oxyphil cells might be an indicator for an elevated risk of parathyroid hyperfunction (3,4).

1.1.1 Production and regulation of the parathyroid hormone

The most bioactive form of the parathyroid hormone is PTH (1-84). It is a straight chain peptide made up of 84 amino acids. The production of the hormone in the chief cells of the parathyroid glands involves a number of processes (Figure 1). First the genetic code of PTH located on chromosome 11 is translated to mRNA-encoding PTH (5). The mRNA then leaves the nucleus where adenosine and uridine rich elements binding proteins (ARE-BPs) bind to AREs of the mRNA. In this process the mRNA is either stabilized or destabilized. Stabilized mRNA is further translated into prepro-PTH in the ribosomes (6,7). The prepro-PTH is then moved into the endoplasmatic reticulum (ER) where it is split into pro-PTH. In the trans-golgi network the pro-PTH is furthermore cleaved into the mature PTH (8). The active form PTH (1-84) is then stored in granules inside of the parathyroid cells. From there, PTH (1-84) is released into the bloodstream as a countermeasure to low a concentration of ionized calcium in the blood (9).

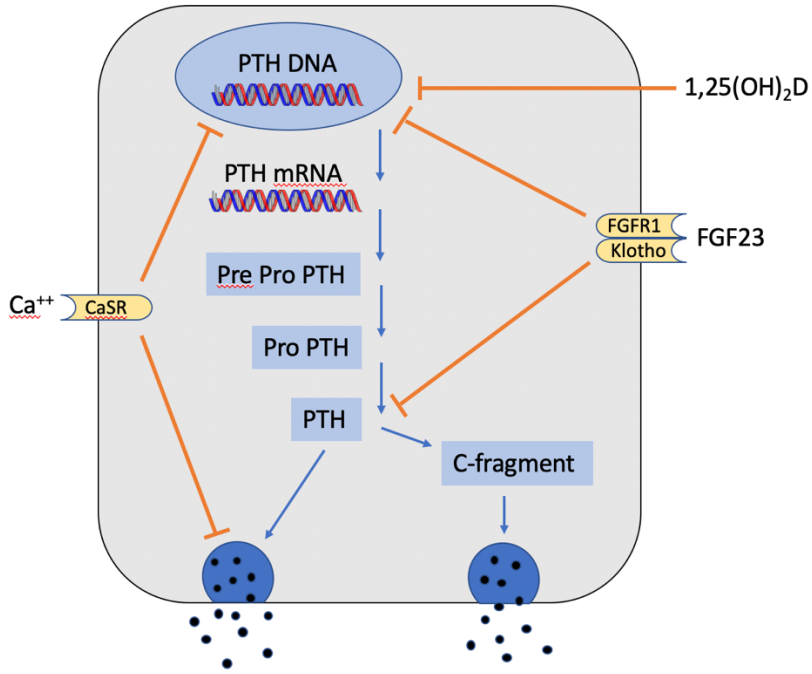

Figure 1: Production of PTH in the chief cells (modified with permission from Goltzman et al., 2018)

Ionized calcium (Ca^{++}) binds to calcium sensitive receptors (CaSR) located at the surface of the parathyroid chief cells and thereby inhibits PTH release. Consequently more PTH is secreted if the concentration of Ca^{++} decreases (5). Through this mechanism the G-protein coupled CaSR is important for quick PTH secretion and furthermore renal reabsorption of

calcium. In case of a sudden period of hypocalcemia the increase of PTH is triggered within one minute and peaks after four to ten minutes (6).
In addition to the active form of the hormone also the level of inactive PTH fragments is increased by enzymatic fragmentation of PTH (1-84). Those fragments have a longer plasma half-life than the active PTH. As a consequence, 80 % of serum PTH consists of inactive fragments (9).
For long term PTH regulation the control of PTH production is important. This is bound to the availability of mRNA-encoding PTH and the levels of $1,25(OH)_2D$. The active form of vitamin D suppresses the rate of the PTH gene transcription and reduces PTH production in doing so. As a consequence, diseases with reduced vitamin D concentrations like chronic kidney disease add to an increased PTH production. Furthermore Ca^{++} concentrations also influence the PTH production directly. Low levels of ionized calcium thereby contribute to increased PTH production. Inversely a high concentration of Ca^{++} decreases PTH fabrication. Regulation of PTH through $1,25(OH)_2D$ and Ca^{++} both include the parathyroid transcription factor, GCMB (5,6)
Furthermore, magnesium binds to the CaSR where it acts like calcium only less potent. When serum levels of magnesium decrease the secretion of PTH is increased. This mechanism works until a serum concentration of 0.5 mM. At lower levels of magnesium, the PTH secretion is reduced. Consequently, a distinct hypomagnesaemia results in low levels of PTH (10).
In recent years further pathways of PTH regulation have been discovered. Those include the fibroblast growth factor 23 (FGF23) that inhibits the expression of mRNA-encoding PTH and the secretion of PTH directly (11). Also lithium, transforming growth factor (TGF-α), prostaglandins and inorganic phosphate (Pi) have been reported to modulate the serum levels of PTH (5).

1.1.2 Functions of PTH

One of the main functions of PTH is to regulate the concentration of calcium in the serum. In case of low ionized calcium sensed by the CaSR, the parathyroid glands release parathyroid hormone into the bloodstream. This leads to an elevation of serum calcium through different pathways.

It directly enhances the calcium reabsorption in the distal nephron and the thick ascending loop of Henle of the kidneys through complex pathways. Moreover, the hormone increases bone resorption by binding to osteoblasts that on the other hand increase the activity of osteoclasts. The rise of PTH furthermore stimulates the production of calcitriol (1,25-dihydroxyvitamin D) in the kidneys which in turn leads to increased intestinal calcium and phosphate uptake (12).

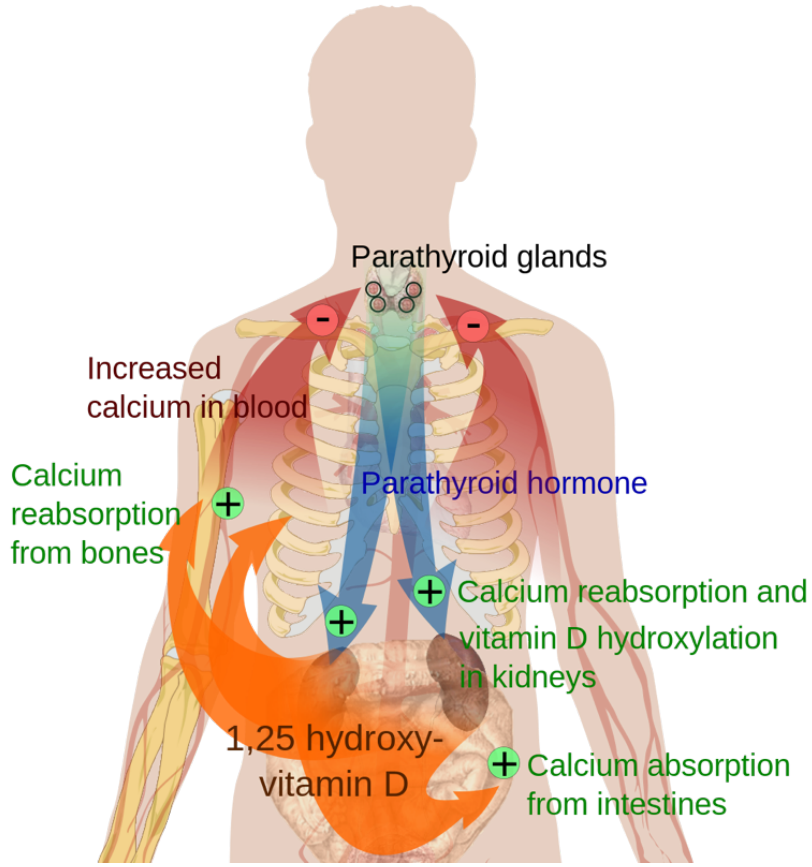

Figure 2: Calcium regulating pathways of PTH (File:Calcium regulation.png. (2022, November 15). *Wikimedia Commons, the free media repository*. Retrieved 17:10, December 20, 2022 from https://commons.wikimedia.org/w/index.php?title=File:Calcium_regulation.png&oldid=706289439.)

1.2 Calcium

Calcium (Ca) is an element essential to many functions of the human body. It plays a crucial part in the transmission of nerve impulses, contraction of muscle fibers, coagulation of blood, hormone secretion, and intercellular adhesion (13). More than 99 % of Ca in the human organism is stored in the bones, mainly as hydroxyapatite. This compound of calcium and phosphate gives the bone its rigidity but also serves as the most important calcium storage. Besides the bone turnover the serum calcium levels are regulated through the intestinal uptake and the renal excretion or reuptake (14).

1.2.1 Calcium homeostasis

The total amount of calcium in the human body is around 1 kilogram in a healthy adult. Of that about 99 % are stored in the bones and less than 1 % (~10 grams) is present as serum calcium. The physiological range of total serum calcium is around 8.8 to 10.4 mg/dl (2.2-2.6 mmol/l). The overall serum calcium thereby consists of 51 % free ionized calcium (Ca^{++}) with a physiological concentration of 4.4 to 5.4 mg/dl (1.10 to 1.35 mmol/l). 40 % is bound to proteins especially albumin and globin. The remaining 9 % are stored in ionic complexes like calcium phosphate, calcium oxalate and calcium carbonate (15).

Only the free ionized calcium is biologically active making the measurement or at least estimation of calcium ions in the serum very important. This is complicated by the fact that the percentage of free ionized calcium can vary depending on the pH value and the protein concentration of the blood. In a state of acidosis, the hydrogen ions compete to bind with serum albumin. Therefore, the concentration of free calcium ions in the serum is elevated in a state of acidosis and lower in alkalosis. Furthermore, the Ca^{++} concentration is decreased if albumin is more abundant and increased in a state of low protein concentration (16).

The total amount of calcium has to be sustained through nutrition since only a limited amount of bone calcium is available for regulating the serum levels of the mineral without harming the bone structure (17). The German nutrition society recommends a daily calcium intake of 1000 mg for healthy adults (18).

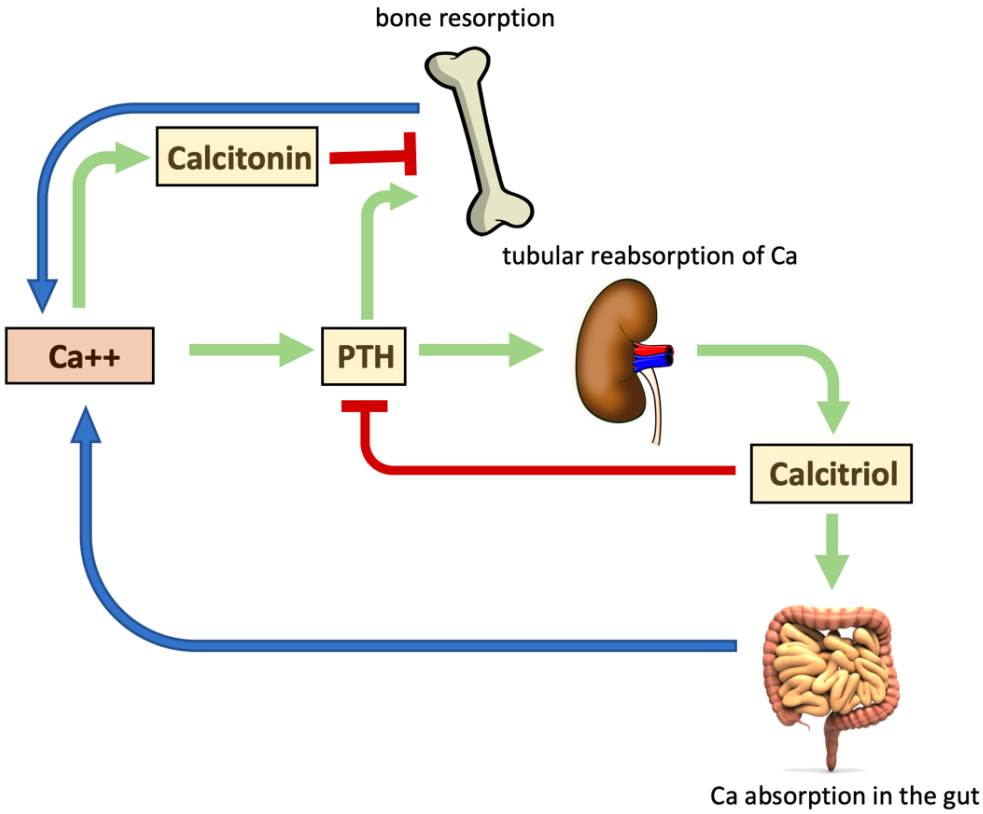

Figure 3: Regulation of calcium (modified from File:Calcium balance 2.jpg. (2021, October 3). *Wikimedia Commons, the free media repository*. Retrieved 19:00, December 20, 2022 from https://commons.wikimedia.org/w/index.php?title=File:Calcium_balance_2.jpg&oldid=595466246.)

1.2.2 Gastrointestinal calcium handling

Calcium is mainly absorbed in the duodenum, jejunum and ileum. There the relative calcium uptake is dependent on the length of the intestinal section and the time that the food takes to pass the particular segment. The calcium absorption in the intestine is based on two mechanisms. The passive paracellular pathway and the active transcellular transport. The paracellular pathway is directly linked to the concentration of calcium in the gut. Furthermore, it is regulated by calcitriol ($1,25(OH)_2D$) which influences the structure of tight junctions thereby promoting the passive uptake of calcium. The active uptake of calcium works by actively absorbing Ca through transient receptor potential vanilloid channels (TRPV6) along its concentration gradient into the apical section of the microvilli. There calcium is bound to calmodulin-actin-myosin I complexes and moved to the basolateral part of the cell. Those complexes can become saturated and thereby limit the calcium uptake. Calcitriol stimulates the production of calbindin which unloads the calmodulin-calcium complexes and makes calmodulin free for further calcium transportation from the microvilli. Thereby $1,25(OH)_2D$ upregulates the active calcium uptake in the intestine (12,13).

1.2.3 Renal calcium handling

In the kidneys free ionized calcium and complexed calcium that is bound to molecules like phosphate or citrate are ultrafiltrable. 10 grams of calcium are filtered daily by a healthy kidney with a GFR of about 100 ml/min. Of those about 98-99 % are reabsorbed leading to a renal calcium excretion of about 100 to 200 ml per day. 60-70 % are reabsorbed in the proximal tubule, 20 % in the loop of Henle, 10 % in the distal convoluted tubule, and 5 % in the collecting duct. Only 5-10 % of the filtered calcium is reabsorbed in the terminal nephron but it is the most important site for the regulation of renal calcium excretion. In the proximal tubule the reabsorption works mainly due to passive mechanisms. Only 10-15 % of the calcium reuptake is through active transportation. This active mechanism is mainly regulated by parathyroid hormone and calcitonin. Reabsorption of calcium in the thick ascending loop of Henle is affected by CaSR found on the basolateral membrane. The inhibition of the receptor leads to a change in the composition of the tight junctions and thereby enhances calcium permeability. Hypercalcemia thereby inhibits calcium reuptake due to CaSR stimulation. Furthermore active reabsorption in the thick ascending loop of Henle is stimulated by PTH and calcitonin (13,19).

1.2.4 Bone turnover

The skeleton has an important structural function and thereby is important for safeguarding the inner organs and serving as muscle attachments to enable movement. As a second important function the bones serve as storage for calcium and phosphate. A healthy bone is always under reconstruction also called remodeling. Thereby the bone is deconstruction by osteoclasts which is followed by osteoblasts forming new bone. This process is needed to adapt the bone structure to mechanical forces or repair microfractures whilst maintaining the size, shape and quality of the human skeleton. Under normal circumstances the resorbed bone is fully replaced by new bone, but this balance can be tipped to either side due to different circumstances (20).

Parathyroid hormone can promote either bone formation or bone resorption. If PTH is given intermittently it stimulates the formation of new bone and if continuously elevated it leads to increased bone resorption (20).

PTH binds to its receptor (PTH1R) on cells of the osteoblastic lineage. This stimulates the presentation of the receptor activator of nuclear factor κ-B (RANK) and the production of osteoprotegerin (OPG) is decreased. The osteoblasts then bind to the membrane receptor RANK of mononuclear osteoclast precursors which stimulates the differentiation of osteoclasts. OPG is a decoy receptor that binds to RANK and thereby inhibits the osteoclast differentiation stimulated by RANK.

In intermittent doses PTH stimulates the formation of bone by increasing OPG and decreasing RANK. Therefore, it is not only important for bone resorption but in general for the constant remodeling of the bone structure which is key to a healthy skeleton (21).

Since bone is primarily made up of hydroxyapatite the resorption of bone releases calcium and phosphate making it an important mechanism to counter regulate hypocalcemia (5,21).

1.2.5 Vitamin D in calcium homeostasis

The active form of vitamin D is synthesized in the human body. As a first step the provitamin 7-dehydrocholesterol is transformed into cholecalciferol under the influence of UV-light in the skin. Cholecalciferol can also be supplied by certain foods and is then resorbed in the intestine. In the further process cholecalciferol is transported into the liver and hydroxylated which results in 25-hydroxyvitamin D also called calcidiol. Ultimately the 1-alpha-hydroxylase in the kidneys generates the active form of vitamin D, calcitriol (1,25-

dihydroxyvitamin D) which is mostly used in the endocrine system to regulate calcium homeostasis (22). PTH promotes the conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D by transcriptional activation of the gene coding for the 1-alpha-hydroxylase in the kidney. Thereby PTH has an important regulatory impact on vitamin D (5). There are also cells that express 1-alpha-hydroxylase in the skin, breast, colon, prostate, lung and many cells of the immune system. In those cells 25-hydroxyvitamin D is also turned into 1,25-dihydroxyvitamin D where it serves no systemic purpose but is rather used as an autocrine cofactor to regulate gene expression. This involves genes that serve a purpose in differentiation, apoptosis or proliferation of the cells. Therefore, the role of vitamin D is far more complex than just the regulation of serum calcium levels. For example, it has been shown that a shortage of vitamin D is linked to an increased number of cardiovascular diseases. Data also suggests an inverse correlation between vitamin D and likelihood of cancer of the colon, ovary and breast. Furthermore people with lower vitamin D levels are more prone to infections (22).

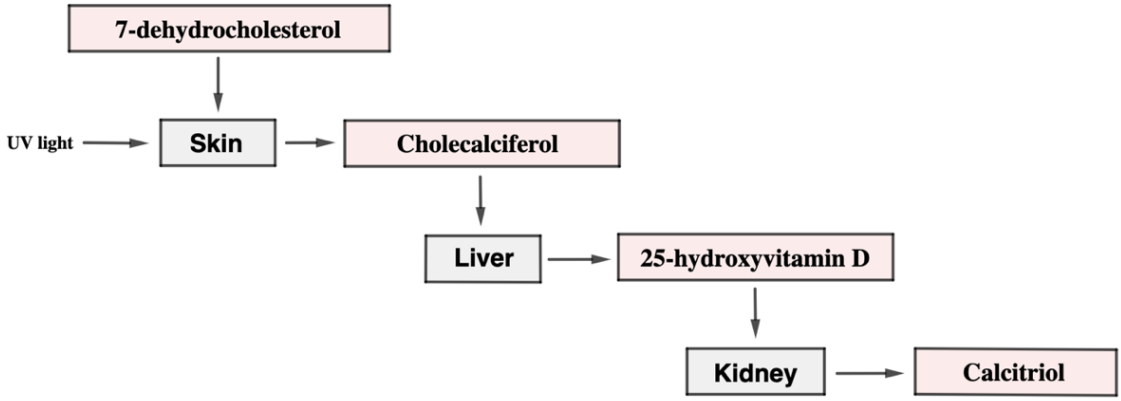

Figure 4: Production of calcitriol in the human body (modified from File:Non-classical role of vitamin D.svg. (2022, February 21). *Wikimedia Commons, the free media repository*. Retrieved 18:49, December 20, 2022 from https://commons.wikimedia.org/w/index.php?title=File:Non-classical_role_of_vitamin_D.svg&oldid=631467181.)

Vitamin D influences calcium levels primarily by increased intestinal resorption along with phosphorus. This is achieved especially by upregulation of the transcellular pathway which has different transport proteins that are sensitive to vitamin D. The transient receptor potential cation channel, subfamily V, member 6 (TRPV6) which is a calcium channel that helps with calcium uptake into the enterocytes. Calbindin 9k which transports the calcium from the luminal side of the cell to its basal side. Furthermore the proteins PMCA1b and

NCX1 which discharge calcium out of the enterocyte into the bloodstream are under the influence of vitamin D (23).
In the kidneys active calcium reabsorption works in a similar manner to the before mentioned intestinal uptake. Calcium is shipped via TRPV5 into the renal epithelial cells, is afterwards transported by calbindin-D_{28K} to the basal part of the cell and then extruded by NCX1 and PMCA1b. It is supposed that the calcium transport proteins TRPV5, calbindin-D_{28K} and NCX1 are under the influence of vitamin D (24).
Furthermore 1,25$(OH)_2$D has an influence on bone mineralization. During times of too little calcium uptake vitamin D has an influence on increased bone resorption and inhibits bone formation (25).

1.2.6 Role of calcitonin in calcium homeostasis

Calcitonin is a peptide hormone produced mainly in the C-cells of the thyroid gland but also in the parathyroid glands and the thymus. Its release is stimulated by high calcium levels in the blood and induces the storage of calcium in the bones. Furthermore, it generates increased renal excretion of phosphate and tubular reabsorption of calcium (16).

1.3 Phosphate

Phosphate plays a vital role in several cellular tasks such as energy metabolism, bone formation and signal transduction but also as component of phospholipids and nucleic acids (26). Less than 1 % of the total phosphate in the human body is contained in serum phosphate. The major part of phosphate is stored in the bones where it is bound to calcium. The serum levels of phosphate have to be tightly controlled within a range of 2.5-4.5 mg/dl to ensure the functioning of its cellular tasks. This balance is controlled by daily dietary uptake, absorption in the gut, renal excretion, bone turnover and the constant exchange of phosphate between intracellular and extracellular compartments (13).

1.3.1 Regulation of phosphate

The gastrointestinal absorption of phosphate occurs primarily in the duodenum and the jejunum. The uptake depends on sodium phosphate cotransporters (Npt2b) that are controlled by the total phosphate intake and 1,25$(OH)_2$D (13).

In the kidneys, 75 % to 85 % of the phosphate filtrated in the glomerulus is reabsorbed in the proximal tubule. The reuptake is controlled by the quantity of sodium phosphate cotransporters (Npt2a, Npt2c and PiT-2) located on the apical membrane of the proximal tubule cells (26). The extent of the renal phosphate reabsorption is influenced greatly by a number of hormones such as PTH and fibroblast growth factor-23 (FGF-23) but also dietary factors (13). PTH decreases the number of cotransporters consequently leading to a decrease of renal reabsorption, thus lower serum phosphate (27). It has been suggested that calcitriol increases the renal reabsorption of phosphate (28). FGF-23 is produced by osteoblasts as response to high levels of serum phosphate. Together with its cofactor (klotho) the released FGF-23 leads to a decrease of sodium phosphate cotransporters in the kidneys. Furthermore, FGF-23 reduces the production of 1alpha-hydroxylase and increases the calcitriol degrading 24-hydroxylase in the kidneys. Since FGF-23 also inhibits the synthesis of PTH, the constellation of those interactions leads to a decreased level of active vitamin D (29,30).

Table 1: Factors that alter the renal regulation of phosphate

Increase Phosphate Absorption	***Decrease Phosphate Absorption***
• *Low-phosphate diet* • *1,25-Vitamin D3* • *Thyroid hormone*	• Parathyroid hormone • Phosphatonins (e.g., FGF23) • High-phosphate diet • Metabolic acidosis • Potassium deficiency • Glucocorticoids • Dopamine • Hypertension • Estrogen

(13)

1.4 Hypoparathyroidism

Hypoparathyroidism is a rare disease defined as an inadequately low parathyroid hormone in comparison to serum levels of ionized calcium or albumin-corrected calcium. However, this also includes the constellation of hypocalcemia and normal (= inadequately low) levels of PTH (31). In comparison pseudohypoparathyroidism is a disease caused by the lack of response to high levels of PTH (receptor defect) and therefore a combination of low calcium and high PTH (32).

The various forms and causes of hypoparathyroidism can be categorized in different ways. One possible classification is to divide them into primary hypoparathyroidism and secondary or acquired hypoparathyroidism. The primary form of hypoparathyroidism is caused by congenital defects of the parathyroid glands mostly due to genetic defects. The far more common group of secondary or acquired hypoparathyroidism is caused by any form of ablation and destruction of the glands as well as impairment of function. Surgery is the most common cause with ca. 75 % of cases. The remaining 25 % are primarily caused by autoimmune/genetic diseases. The remainder are caused by infiltrative disorders like metastastic diseases or the deposition of iron or copper (9). In the following parts of this thesis, the disease will be grouped into postsurgical and nonsurgical hypoparathyroidism.

The prevalence of hypoparathyroidism was calculated by Clarke et al. to be about 37/100 000 person-years based on a study from the United States which estimated the prevalence of hypoparathyroidism based on the analysis of a large health plan claims database (9,33).

1.4.1 Postsurgical hypoparathyroidism

Hypoparathyroidism after anterior neck surgery is the most common cause of hypoparathyroidism which makes the disease also more common in older women since the female population has a higher risk of needing thyroidectomy (31). A Danish study estimated the prevalence of postsurgical hypoparathyroidism to be 22/100 000 (34).
Postsurgical hypoparathyroidism has no uniform definition. For this reason, the reported incidence varies. Nevertheless, a typical definition is the combination of hypocalcemia (< 2.0 mmol/l or < 8.0 mg/dl) with low PTH under 15 ng/l or unsuitably normal PTH. Since

initial postsurgical hypoparathyroidism is not always a permanent state, chronic hypoparathyroidism is only diagnosed 6 or 12 month after surgery (32).
The risk of post-surgical hypoparathyroidism varies strongly with the experience of the surgeon. The calculated risk reaches from 0.1 % to 5.6 % for permanent post-surgical hypoparathyroidism and from 25.4 % to 83 % for transient hypoparathyroidism (9).

1.4.2 Nonsurgical hypoparathyroidism

Nonsurgical hypoparathyroidism that does not occur as part of a syndrome but as solitary endocrinopathy is called isolated hypoparathyroidism. The prevalence was estimated to be 2.3/100 000 (35). In many cases hereditary genetic abnormalities are known but, in the majority, the underlying cause is unknown. Autosomal inheritable cases of isolated hypoparathyroidism can be liked to mutations in the PTH, GCMB or CaSR encoding genes. Besides those autosomal etiologies the X-linked recessive hypoparathyroidism is known (36). Furthermore, hypoparathyroidism can occur due to different mechanisms that impair the physiological functioning of the parathyroid glands. Magnesium stimulates the CaSR and in consequence inhibits PTH production. Therefore, hypomagnesemia can be linked to low PTH levels. Also disorders such as Wilson´s disease, hemochromatosis or repetitive transfusions for diseases such as Thalassemia major can induce hypoparathyroidism by the accumulation of copper or iron respectively in the glands. Finally the disease can be caused by infiltrating tumors or ionizing radiation (32).

1.4.3 Hypoparathyroidism as part of a syndrome

There are many genetic mutations causing hypoparathyroidism as part of a syndrome. Those mutations can be tested, not only to find the root cause but also to adjust treatment or diagnose mutation-carrying family members (9).
One of the more well-known syndromes is DiGeorge syndrome affecting around 1 in 4 000-5 000 live births. In most cases DiGeorge syndrome is linked to a de novo mutation causing a microdeletion of the 22q11.21-q11.23 chromosomal region. The typical presentation of the syndrome is thymic aplasia and following immunodeficiency, congenital heart defects, cleft palate, facial abnormalities, renal dysfunction and in 60 % of cases hypoparathyroidism (36). Other syndromes that include hypoparathyroidism are autoimmune polyglandular syndrome type 1; coloboma-heart anomaly-choanal atresia-retardation-genital-ear anomalies

syndrome; Kenny-Caffey syndrome; Barakat syndrome; Dubowitz syndrome; Bartter syndrome type 5; Kearns-Sayre syndrome; mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes syndrome; and the mitochondrial trifunctional protein deficiency syndrome (9).

1.4.4 Symptoms of hypoparathyroidism

The clinical manifestations of hypoparathyroidism range from asymptomatic to life-threatening. Typical presentations are mostly caused by hypocalcemia leading to paresthesia, muscle cramps, extended QT interval but also to serious complications like arrythmias, laryngospasm, and seizures (31). Hypocalcemia interferes with the physiological depolarization of neurons. The neurological manifestations can be divided into those caused by increased irritability of sensory neurons and those caused by motor neurons. Paresthesia in the peri-oral region or in the extremities is linked to the sensory neurons. Muscle spasms or tetany are caused by the more easily depolarized sensory neurons. Since the spasms can reach from light twitching of the forearm, hand and distal leg called carpopedal spasms to laryngospasms which have to be considered as life-threatening it is important to recognize the clinical signs as soon as possible and evaluate the possibility of hypocalcemia as cause of stridor or even apnea without clear trigger (37,38).

Complications of nonsurgical hypoparathyroidism

A Danish study compared the risk of a multitude of complications in patients with nonsurgical hypoparathyroidism to a healthy control population. This study showed an increased risk of cataract (HR 4.21; 95 % CI, 2.13-8.34). The number of renal insufficiencies was six times higher compared to controls (HR 6.01; 95 % CI, 2.45-14.75). The general risk of cardiovascular disease was nearly doubled (HR 1.91; 95 % CI, 1.29-2.81). This includes a significantly increased risk of ischemic heart disease (HR 2.01; 95 % CI, 2.01-3.09) and a marginally higher risk of strokes (HR 1.84; 95 % CI, 0.95-3.54). The risk of arrythmia was also increased but the risk of cardiac arrest and acute myocardial infarct were not significantly different. Furthermore, patients had an elevated risk of suffering seizures (HR 10.05; 95 % CI, 5.39-18.72) or any neuropsychiatric disorder (HR 2.45; 95 % CI, 1.78-3.35). The total risk of cancer was lower in patients than in controls (HR 0.44; 95% CI, 0.24-0.28). Overall risk of fractures was not increased (HR 1.40; 95 % CI, 0.93-2.11) but patients had a significantly higher risk of upper and lower arm fractures compared to controls. This is

thought to be due to the increased risk of seizures and cataract increasing the risk of falls. Furthermore, patients were significantly more likely to suffer an infection compared to the healthy control population (HR 2.38; 95 % CI, 1.38-4.31). Especially hospitalization due to upper airway infections and infections of the urinary tract were increased (35).

Table 2: Risk of different complications linked to non-surgical hypoparathyroidism

complication	*hazard ratio*	*95 % CI*
cataract	4.21	2.13-8.34
renal insufficiencies	6.01	2.45-14.75
risk of cardiovascular disease	1.91	1.29-2.81
ischemic heart disease	2.01	2.01-3.09
strokes	1.84	0.95-3.54
seizures	10.05	5.39-18.72
neuropsychiatric disorder	2.45	1.78-3.35
cancer	0.44	0.24-0.28
fractures	1.40	0.93-2.11
infection	2.38	1.38-4.31

(35)

Complications/comorbidities of postsurgical hypoparathyroidism

Another Danish study analyzed the risk of different manifestations in patients with postsurgical hypoparathyroidism. The overall risk of fractures was not different in the patient group compared to the healthy control group (HR 1.03; 95 % CI 0.83-1.29). In detail, patients had a significantly lower risk of fractures at the upper extremity. The risk of cataract was not increased (HR_{crude} 1.17; 95 % CI 0.66-2.09). The incidence of depression or bipolar affective disorder was significantly higher. Even after adjusting for preexisting diagnosis, patients had a twofold higher risk than controls. Also, the risk of being hospitalized with infections was significantly higher (HR 1.42; 95 % CI 1.20-1.67) (39).

In another Danish study, the risk of cardiovascular and renal complications was evaluated. In this study, overall mortality of patients with postsurgical hypoparathyroidism was not increased. The diagnosis of cardiovascular disease (CVD) before anterior neck surgery and diagnosis of CVD and ischemic heart disease (IHD) during the follow-up was significantly higher in in patients. When adjusted for preexisting CVD, the risk of hospitalization due to IHD or CVD was no longer increased. Also, the risk of cardiac arrythmias was only borderline increased and after adjusting for prevalent CVD and diabetes no longer

significantly elevated. The rate of renal complications in form of calcifications or renal insufficiency was significantly increased (HR 4.31; 95 % CI 2.84-6.52). Even adjusted for a medical history of seizures the rate of hospitalization due to seizures was significantly higher in patients than in controls (HR 3.82; 95 % CI 2.15-6.79) (34).

Table 3: Risk of different complications linked to post-surgical hypoparathyroidism

complication	*hazard ratio*	*95 % CI*
fractures	1.03	0.83-1.29
cataract	1.17	0.66-2.09
infections	1.42	1.20-1.67
renal complications	4.31	2.84-6.52
hospitalization due to seizures	3.82	2.15-6.79

(34,39)

1.4.5 Diagnosis

Typical signs of hypoparathyroidism include low calcium levels, hyperphosphatemia and low or inadequately low PTH. In comparison, pseudohypoparathyroidism is associated with high levels of PTH. In addition, the levels of 1,25-dihydroxyvitamin D and alkaline phosphate activity, a marker for bone turnover, are mostly low or in the lower normal range. For the right diagnosis it is important to determine the correct levels of PTH. To measure PTH in the blood, there are different tests on the market. However, some of those may have problems detecting only the amount of functional PTH (1-84). Especially in rare forms that are accompanied by reduced activity of PTH this can lead to confusion. Furthermore, genetic testing can be done to differentiate between the many causes of hypoparathyroidism (9).

To help with the detection of increased motor neuron irritability caused by hypocalcemia in everyday clinical practice Chvostek sign and Trousseau signs are used. Chvostek sign is triggered by tapping the facial nerve in front of the ear. In case of severe hypocalcemia, a short contraction of the ipsilateral facial muscles is triggered that causes a twitching of the upper lip, nose and other locations of the face.

The Trousseau sign is provoked by placing the cuff of a blood pressure measurement device around the patients arm and inflating it above the systolic blood pressure for three minutes. If this results in a painful flexion of the wrist and metacarpophalangeal joints, simultaneous extension of the proximal and distal interphalangeal joints as well as an abduction of the fingers a hypocalcemic state is likely (37).

1.5 Therapy

1.5.1 Conventional therapy

In acute situations when hypoparathyroidism presents with seizures and tetany due to low calcium levels, 10 % calcium gluconate is infused over 10 to 15 minutes. The intravenous therapy is then often continued while the oral therapy is started to lower the risk of repeating hypocalcemia. Intravenously administered calcium should always occur during cardiac monitoring due to the risk of arrhythmia in consequence of fast calcium alterations.

The long-term treatment of the disease is normally handled with vitamin D and a form of calcium supplementation to reach blood calcium levels at the lower normal limit or slightly below. This is to reduce the renal calcium excretion and therefore the risk of nephrocalcinosis with the possible consequence of renal insufficiency.

There are different supplements available for treatment. Calcium carbonate is widely available but needs a low gastric pH for sufficient absorption. Therefore, patients with medication that blocks the acid production in the stomach should receive calcium citrate as supplementation. This form is not dependent on an acidic environment, but one should bear in mind that calcium citrate interacts with the uptake of levothyroxine medication.

Calcitriol and alfacalcidol are preferred as active vitamin D supplementation since they have already been activated by the 1α-hydroxylase - which is a process dependent on the presence of PTH. Native vitamin D (chole-/ergocalciferol) is usually required as well.

Hypomagnesemia in patients with hypoparathyroidism is not uncommon since magnesium homeostasis is linked to PTH. Consequently, magnesium supplementation is often beneficial as additional therapy (31).

Table 4: Calcium supplementation

Medication	*Formulation*	*Route of administration*	*Administration for adults*	*Comment*
Calcium				
Calcium gluconate 10 %	9.3 % elemental calcium	i.v.	Bolus: 10-20 mg over the time of 10-15 minutes Continuous: 1.25 mg of elemental calcium per kilogram of bodyweight per hour	ECG monitoring

Calcium chloride 10 %	27.0 % elemental calcium	central venous catheter	Bolus: 5-10 ml over a time of 5-10 minutes	ECG monitoring
Calcium carbonate		oral	0.5-2 g of elemental calcium daily, given in 2-4 doses	should be taken with food to improve absorption and to function as phosphate binder
Calcium citrate		oral	0.5-2 g of elemental calcium daily, given in 2-4 doses	should be taken with food
Calcium glubionate		oral	0.5-2 g of elemental calcium daily, given in 2-4 doses	should be taken with food
Vitamin D				
Calcitriol		oral or i.v.	0.25-3 μg/day divided into 2-3 doses per day	
Ergocalciferol		oral	400-4000 IU/day in combination with calcitriol 10000-100000 IU/day without calcitriol	25-hydroxyvitamin D target: 20-60 ng/ml with calcitriol; >80 ng/ml without calcitriol
Cholecalciferol		oral		
Magnesium				
Magnesium sulfate	492 mg of elemental magnesium per 1 ml of fluid	i.v.	Bolus: 1-2 g over a time of 2-15 minutes Continuous: 4-8 g	ECG monitoring
Magnesium oxide		oral	250-1000 mg of elemental magnesium daily given in 2-4 doses	

(31)

1.5.2 Hormone replacement therapy

Different to most hormone deficiencies, hypoparathyroidism is usually not treated with hormone substitution by default because of the high costs of the available medications. Treatment with recombinant human PTH in Europe is granted under the stipulation that the condition could not be managed with the conventional therapy elaborated in the previous section (31).

It has been shown that the treatment with PTH 1-34 or PTH 1-84 that is administered as a subcutaneous injection once or twice daily reaches an sufficient therapeutic effect in most patients (40,41). This therapy has different effects. Besides the main effect of raising calcium concentration, the phosphate levels in the blood have been reported to be reduced under hormone substitution. This might have a positive effect on the occurrence of ectopic calcifications. Having said this, the effects on renal calcification are yet to be fully determined since there are many different factors that determine the risk of calcification in the kidneys. Bone turnover is elevated with different effects on bone structure like increased cancellous bone volume, increased number of bone trabeculae but also an increased porosity of the cortical bone. Due to the increased bone turnover, a termination of the substitutional therapy should be done gradually to prevent complications of serious hypocalcemia (31).

Table 5: Hormone replacement therapy

Medication	*Formulation*	*Route of administration*	*Administration for adults*	*Comment*
Calcium				
PTH 1-84	25, 50, 75 or 100 µg	subcutaneous	Start of therapy with 50 µg/day and dosage adaptation every 4 weeks by 25 µg	Regular blood tests

(31)

1.6 Impact of Ca, Vitamin D, PTH and phosphate on the cardiovascular system

Muscle contraction is dependent on alterations of calcium concentration. In resting periods calcium is stored inside the sarcoplasmic reticulum leading to a low level of intracellular calcium. Through stimulation the stored calcium ions are released and consequently elevate

the calcium concentration of the sarcoplasm. This allows the binding of actin and myosin which in turn paves the way for muscle contraction (42). It is known that the function of cardiac muscle fibers is partly different from skeletal muscle fibers. This results in a direct correlation between the calcium concentration of the extracellular fluid and the strength of cardiac muscle contraction. A correlation that skeletal muscle fibers do not have. This relationship of cardiac contractility and calcium concentration is thought to be because of the direct correlation of the calcium concentration in the t-tubules and the extracellular calcium concentration (43). It is also assumed that calcium plays an important role in regulating the rhythm of the heart by influencing the cardiac pacemaker tissue (44).

Vitamin D also seems to have a direct impact on the cardiovascular system. In 1983 a receptor for 1,25-dihydroxyvitamin D3 was already detected in the myocardial cells. In 1987 a study on rat hearts analyzed the effect of this discovery by depleting rats of vitamin D3 for nine weeks. After this time the contractility of ventricular and vascular muscle was significantly enhanced. This effect could not be prevented by maintaining a normocalcemic state which suggests a calcium independent influence of vitamin D3 on the cardiac function. Also, vascular contractile function was measured by analyzing the response of aortic rings of the vitamin D3 deficient and sufficient rats to norepinephrine. The contractile response was significantly higher in vitamin D3 deficient rats. Furthermore, the blood pressure increased significantly in vitamin D3 deficient rats compared to those with sufficient vitamin D3 intake. This elevation of blood pressure normalized after eight weeks (45). This data corresponds with a study by Tishkoff et. al. that analyzed the interaction of vitamin D with the cardiac myocytes of adult mice and compared the effects between the wild-type and vitamin D receptor knockout mice. They observed that the rate of contraction and relaxation was significantly increased in the myocytes of knockout mice indicating hypercontractility in absence of vitamin D or the VDR (46). Also cardiac hypertrophy and fibrosis were linked to vitamin D deficiency in studies with VDR knockout mice (47).

1.6.1 Influence of PTH on the cardiovascular system

It has been shown that there is a direct link between PTH and the cardiovascular system. The interaction of PTH and the cardiovascular system has already been suggested in 1925 when PTH was described to have a hypotensive effect (48,49). In 1993 a study discovered the

expression of parathyroid hormone related peptide in the human heart. This already suggested an autocrine function of PTH-rP on the heart (50).

PTH has a different effect on adult cardiac myocytes or neonatal cardiac myocytes. In neonates the PTH increases the adenyl cyclase activity and thereby leads to cAMP-dependent Ca^{2+} influx. In adult cardiac myocytes PTH seems to have an indirect influence by stimulating the protein kinase C also resulting in an increased Ca^{2+} inflow (48).

Those cellular pathways lead to different effects of PTH on the cardiovascular system. PTH inhibits the contractile effects that the stimulation of β-adrenoceptors has on the cardiac muscle cells. This is achieved by activation of a protein kinase C-dependent activation of a phosphodiesterase that in turn decreases the accumulation of cAMP in the cell. Furthermore, increased levels of PTH have been linked to myocardial hypertrophy which is thought to be due to increased protein synthesis or elevated cellular protein mass (51,52).

PTH also has an influence on smooth muscle cells. In the cardiovascular system the hormone especially has a vasodilatory effect by directly influencing the smooth muscle cells of the blood vessels. Thereby it has been shown to decrease blood pressure. It has been suggested that this effect is based on an cAMP-dependent reduction of calcium influx through L-type Ca^{2+} channels (48).

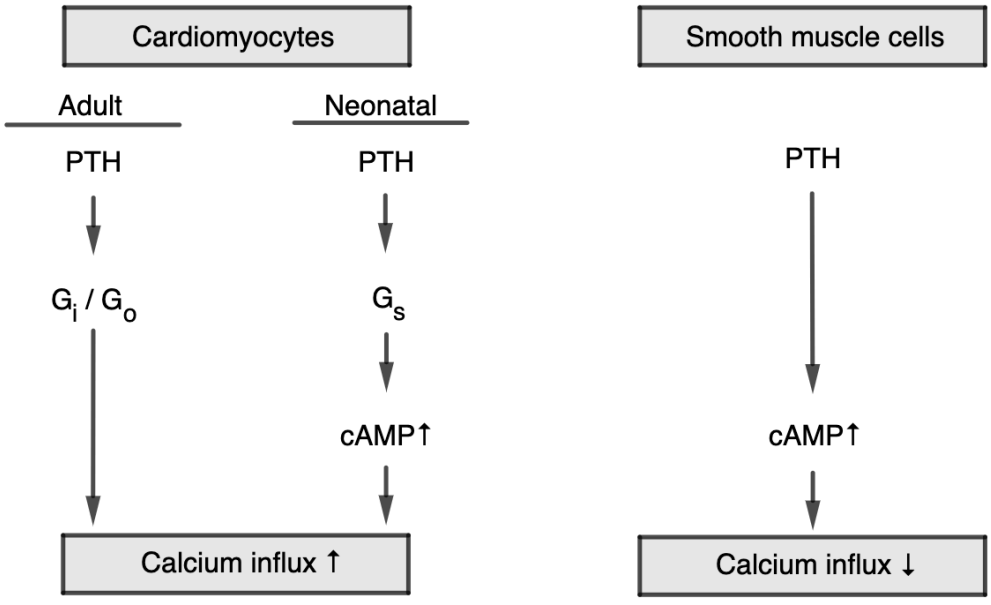

Figure 5: Impact of PTH on the calcium influx in muscle cells (modified with permission from Schlüter et al., 1998) (48)

The parathyroid hormone-related peptide (PTH-rP) is a peptide structurally similar to PTH. It is expressed in different tissues of the cardiovascular system like smooth muscle cells, endothelial cells and atrial cardiomyocytes. Those are also the target cells of PTH-rP with the exception of endothelial cells. Due to the similarities between PTH and PTH-rP the related protein can bind to the same receptors as PTH therefore causing similar effects in classical target cells like chondrocytes, kidney cells or osteoblasts. In addition, PTH-rP also has effects on the cardiovascular system that include vasodilation, beating activity of the heart, protein synthesis and cAMP accumulation. The lowering effects of PTH-rP on blood pressure even exceed those of PTH (48).

1.6.2 Impact of phosphate on the cardiovascular system

Hypoparathyroidism is associated with increased serum levels of phosphate and raised reabsorption of phosphate in the renal tubules (9). Like patients suffering from hypoparathyroidism also patients with renal insufficiency show hyperphosphatemia and hypocalcemia but in contrast PTH is often elevated as a result (53). Therefore, studies on the consequences of hypocalcemia and hyperphosphatemia in renal insufficiency are often compared to the manifestations of hypoparathyroidism.

A study included 39 patients with end-stage renal disease and evaluated the coronary-artery calcification using electron-beam computed tomography and compared the data to 60 healthy individuals that were age matched. The results showed an elevated serum phosphorus concentration and a higher calcium-phosphorus ion product in patients with coronary artery calcification compared to those without calcification (54). Another study analyzed patients with normal kidney function and found a significant association of elevated phosphorus concentration and left ventricular hypertrophy (55). Dhingra et al. investigated if there is an association between elevated phosphorus concentration in the serum, increased calcium-phosphorus product and increased mortality due to cardiovascular events that has been shown in patients with chronic kidney disease (CKD) is also detectable in individuals with normal kidney function and without pre-existing cardiovascular disease. Therefore, the study included data from 3368 Framingham Offspring study participants without CVD or CKD. The results showed a significant correlation of elevated phosphorus levels and cardiovascular events (56). A study published in 2001 already found a significant correlation between increased phosphorus levels and death due to cardiovascular events. More specifically patients with CKD and PO_4 >6.5 mg/dl had a 41 % higher risk of coronary

artery disease resulting in death compared to patients with a PO_4 concentration between 2.4 and 6.5 mg/dl (57).

2 Materials and Methods

This thesis was created by performing a literature search and comparison of different literature. For the most part the literature search tool “PubMed” was used. The search was performed by searching for a combination of keywords like “hypoparathyroidism”, “heart”, “cardiovascular”, “neurological”, “seizures” or “basal ganglia calcification” and many more. Recent studies of the past 10 years were preferred. For basic knowledge and introductory informations, textbooks for endocrinology were used.

3 Results

3.1 Cardiovascular manifestations of hypoparathyroidism

Hypoparathyroidism is linked to an elevated risk of cardiovascular disease. Underbjerg et al. found a borderline significantly increased risk of strokes and a significantly higher risk of ischemic heart disease and arrhythmia (35). The risk of arrythmia is thought to be based on a prolongation of the QT interval caused by low calcium levels. It also seems like PTH has an direct impact on the cardiovascular system (58). In comparison a retrospective cohort study analyzed the data of 8097 individuals with chronic hypoparathyroidism and compared it to 40485 controls. The results showed a significantly higher risk of atrial fibrillation, cerebrovascular disease, coronary artery disease, myocardial infarction, heart failure, peripheral vascular disease, stroke and tachyarrhythmia (59).

Several studies evaluate the risk of cardiovascular disease in patients with hypocalcemia and especially hypoparathyroidism. Thereby the risk of cardiovascular disease seems to be different in the various forms of hypoparathyroidism. In the following part the statistics of cardiovascular disease associated with postsurgical and non-surgical hypoparathyroidism will be compared.

In 2015 Underbjerg et. al. analyzed the data of patients with nonsurgical hypoparathyroidism. The information was collected from the Danish National Hospital Patient Registry. The data of 180 patients diagnosed with nonsurgical hypoparathyroidism was included and compared to 540 healthy controls. From the 180 individuals 38 (21.1 %) had a genetic diagnosis of the underlying cause. A total of 22 suffered from DiGeorge Syndrome, 13 were diagnosed with autosomal dominant hypoparathyroidism, 2 had a mutation of the AIRE gene and 1 was categorized as familial isolated hypoparathyroidism. The results of the study showed that patients with nonsurgical hypoparathyroidism had a significantly increased risk of suffering from any cardiovascular disease compared to controls (HR 1.91; 95 % CI, 1.29-2.81). The term cardiovascular disease thereby includes ischemic diseases of the heart and strokes. In detail the risk of ischemic heart disease was significantly increased (HR 2.01; 95 % CI, 2.01-3.09) whereas the risk of cases suffering a stroke was only elevated with borderline significance (HR 1.84; 95 % CI, 0.5-3.54). Furthermore, patient data showed a borderline increased risk of arrhythmia (HR 1.78; 95 %

CI, 0.96-3.30). The chance of acute myocardial infarction and cardiac arrest was not significantly different (see Table 6) (35).

Table 6: Cardiovascular complications of nonsurgical hypoparathyroidism

Cardiovascular disease	*Cases (n = 180)*	*Controls (n = 540)*	*p*	*HR (95 % CI)*
Any cardiovascular disease	**42 (23,3)**	**66 (12,2)**	**0,01**	**1,91 (1,29-2,81)**
Ischemic heart disease	**35 (19,4)**	**52 (9,6)**	**0,01**	**2,01 (1,31-3,09)**
Stroke	**15 (8,3)**	**22 (4,1)**	**0,03**	**1,84 (0,95-3,54)**
Arrhythmia	**17 (9,4)**	**25 (4,6)**	**0,03**	**1,78 (0,96-3,30)**
Acute myocardial infarction	10 (5,6)	22 (4,1)	0,41	1,29 (0,61-2,72)
Cardiac arrest	2 (1,1)	2 (0,37)	0,26	2,84 (0,40-20,13)

(35)

In 2013 Underbjerg et. al. compared the data of 688 patients diagnosed with postsurgical hypoparathyroidism to 2064 age and gender matched controls. For this study postsurgical hypoparathyroidism was defined as hypocalcemia below the lower reference level and inappropriately low concentrations of PTH that caused treatment with calcium and/or vitamin D analogs for more than 6 months after neck surgery. Patients with missing medical data, surgery before 1988 and those with a diagnosis of Multiple endocrine neoplasia, parathyroid cancer and/or thyroid cancer were excluded as well as patients with hypoparathyroidism due to radiation. As shown in Table 7, the raw data suggests that significantly more patients suffered from ischemic heart disease or any cardiovascular disease (34).

Table 7: Cardiovascular complications of postsurgical hypoparathyroidism (not adjusted)

Cardiovascular disease	*Cases (n = 688)*	*Controls (n = 2064)*	*p*	*HR (95 % CI)*
Any cardiovascular disease	**101 (14.7 %)**	**221 (10.7 %)**	**<0.01**	**-**
Ischemic heart disease	**77 (11.2 %)**	**162 (7.8 %)**	**0.01**	**-**
Stroke	35 (5.1 %)	80 (3.9 %)	0.19	-
Arrhythmia	50 (7.2 %)	110 (5.3 %)	0.07	-
Acute myocardial infarction	18 (2.6 %)	52 (2.5 %)	0,89	-
Arrhythmia-induced deaths	2 (0.3 %)	8 (0,4 %)	1.00	-

(34)

To further evaluate those results shown in Table 7, the prior medical data of the patients and controls was analyzed for cardiovascular disease before neck surgery. The comparison

showed that the patients already had a significantly ($p < 0,01$) higher rate of cardiovascular disease before the surgery that lead to hypoparathyroidism (n = 63; 9,2 %) compared to controls (n = 102; 4,9 %). Therefore, if adjusted for cardiovascular problems that manifested before the surgery that caused the onset of hypoparathyroidism and/or diabetes, the risk was not elevated anymore. Also, the initially borderline significantly increased risk of cardiac arrhythmias was no longer elevated if adjusted for preexisting cardiovascular disease (34).

Table 8: Cardiovascular complications of postsurgical hypoparathyroidism (adjusted)

Cardiovascular disease	*Hazard ratio*	*HR (95 % CI)*
Cardiac arrhythmias[a]	1,11	0,79-1,57
Acute myocardial infarction[b]	0,77	0,44-1,34
Stroke[b]	1,09	0,73-1,64
Cardiac arrest[b]	0,68	0,15-3,23
Ischemic heart disease[b]	1,09	0,83-1,45

[a]adjusted for prior cardiovascular disease.

[b]adjusted for prior cardiovascular disease and diabetes.

(34)

In 2016 Underbjerg et al. compared the risk of cardiovascular manifestations in patients with pseudohypoparathyroidism and pseudopseudohypoparathyroidism to the risk for a healthy control population. The patient data was acquired through the Danish National Patient Registry a prescription database. A total of 60 patients were included in the study. Of those 33 suffered from pseudohypoparathyroidism type 1A, two from 1B, four from type 2 and two patients were diagnosed with pseudopseudohypoparathyroidism. The remaining 19 patients had pseudohypoparathyroidism, but the disease was not further specified. At the time of diagnosis, the plasma levels of PTH were elevated (mean 32.5 pmol/l) and the concentration of ionized calcium was low (mean 0.94 mmol/l). The data showed no significant differences in cardiovascular complications between patients and healthy controls (see Table 4) (60).

Table 9: Cardiovascular complications of pseudo- and pseudopseudo hypoparathyroidism

Cardiovascular disease	*Cases (n = 60)*	*Controls (n = 180)*	*p*	*HR (95 % CI)*
Any cardiovascular disease	0 (0 %)	10 (5.6 %)	0,34	-
Ischemic heart disease	0 (0 %)	5 (2.8 %)	0.34	-
Stroke	0 (0 %)	2 (1.1 %)	1.00	-

Arrhythmia	2 (3.3 %)	6 (3.3 %)	1.00	1.19 (0.23-6.2)
Acute myocardial infarct	0 (0 %)	3 (1.6 %)	0.58	-

(60)

3.1.1 Cardiovascular autonomic neuropathy

Cardiovascular autonomic neuropathy (CAN) is an impairment of the autonomic control of the cardiovascular system. It is often reported in diabetics where it is linked to increased exhaustion and mortality based on an elevated risk of cardiac arrythmias.
In 2019 Tabacco et al. analyzed the data of 51 patients with postsurgical hypoparathyroidism under calcium and calcitriol treatment and compared it to a control group of 43 individuals who had also undergone thyroidectomy but did not suffer any abnormalities concerning PTH, calcium or phosphate. The goal of this study was to determine if levels of PTH, calcium or phosphate could be linked to cardiovascular autonomic neuropathy (CAN). To determine CAN, four tests were performed: ratio of heart rate in expiration to inspiration, heart rate response lying-to-standing, heart rate reaction to Valsalva maneuver and the change of the blood pressure when standing (orthostatic hypotension). If one of the heart rate related tests was positive, the patient would be considered to have early CAN and two or more positive tests were defined as definite CAN. If furthermore orthostatic hypotension was present, the individuals would be categorized as patients with advanced CAN.
Of the patients with hypoparathyroidism, 78 % were diagnosed with CAN compared to 23 % of the individuals without hypoparathyroidism ($p = <0.001$). Definite CAN was present in 43 % of the hypoparathyoidism group and in 2 % of the controls ($p = <0.001$). Orthostatic hypotension was not diagnosed in any patients or controls and therefore no individuals were categorized as advanced CAN. As shown in Table 10, the data suggests a significant correlation between low albumin-adjusted serum calcium (<8.5 mg/dL) and definite CAN with an OR 13.62 (95 % CI, 2.12-149.84). Association with serum phosphate, PTH or vitamin D were not found. Further analysis of the data showed a correlation of disease duration and definite CAN with OR 1.10 (95 % CI, 1.00-1.24). The data of this study suggests a clear connection between CAN and hypoparathyroidism (61).

Table 10: Correlation of CAN with different variables

Variable	*OR*	*95 % CI*
<8.5 mg/dL Albumin-adjusted serum calcium	**13.62**	**2.12-14.84**
disease duration	**1.10**	**1.00-1.24**
PTH serum concentration	0.99	0.85-1.15
Phosphate serum concentration	2.08	0.78-6.43
Urinary calcium	1.00	0.99-1.00
TSH	0.69	0.29-1.49
25 (OH) vitamin D	1.08	0.99-1.19
Age	1.02	0.95-1.10
Sex	14.31	0.36-744.01

(61)

In patients with diabetes, CAN has been suggested to be a significant and independent factor for increased cardiovascular mortality and furthermore, high morbidity and poor life quality (62). For patients with hypoparathyroidism it might therefore be part of the reason why overall mortality may be increased. Since the rate of CAN correlated with lower concentrations of calcium, Tabacco et al. suggests that the current method of therapy to restore calcium levels only to the lower limit of the physiological range might be counterproductive and could potentially increase the risk of CAN for those patients (61).

In 2020 Tabacco et al. further analyzed the connection between CAN and decreased quality of life (QoL) which is based on fatigue, muscle spasms, pain, “brain fog”, limited ability to concentrate, depression, and anxiety. The study included 48 individuals with chronic postsurgical hypoparathyroidism and compared them to 38 subjects without any problems with calcium homeostasis who had undergone thyroidectomy. The 48 patients with hypoparathyroidism were divided into groups. 10 (21 %) without CAN, 19 (39 %) with early CAN and 19 (39 %) with definite CAN. Evaluated were the RAND 36-Item Short Form (SF-36) to evaluate the QoL by assessing the physical (PCS) and mental (MCS) health as well as a fatigue score. The data showed that the fatigue score of the patients was lower than that of those individuals without hypoparathyroidism (44.5 IQR:9 compared to 38.5 IQR:12.3, p=0.031). Between the patients with hypoparathyroidism, the individuals with definite CAN had a more severe fatigue score than those without CAN (p=0.005). This association might further explain the frequently reported fatigue of patients with postsurgical

hypoparathyroidism. The values of PCS, MCS and the total SF-36 score were not significantly different (see Table 11) (63).

Table 11: Quality of life associated with cardiovascular autonomic neuropathy

	No CAN (n=10)	*Early CAN (n=19)*	*Definite CAN (n=19)*	*P-value*
PCS, median (IQR)	355 (42.4)	290 (158)	270 (114)	0.054
MCS, median (IQR)	345 (126)	293 (177)	241 (137)	0.257
SF-36 total, median (IQR)	687 (197)	588 (362)	500 (256)	0.093
Fatigue score, median (IQR)	**46 (2.5)**	**42 (12)**	**45 (7.5)**	**0.005**

(63)

3.1.2 Hypocalcemic cardiomyopathy

The lack of calcium in the blood is a rare but well recognized cause of dilated cardiomyopathy (CMP). Although the importance of calcium for the functioning of the heart muscle is well known, the exact pathophysiological pathways that lead to hypocalcemic CMP are still not well understood. Hypocalcemic CMP is more often found in children where it is mostly caused by profound vitamin D deficiency/rickets. Only a few cases of adults suffering from hypocalcemic CMP have been reported. The most common underlying cause of the hypocalcemia in adults is hypoparathyroidism (64).

To analyze the data of patients with hypocalcemic CMP, a study by Válek et al. searched for existing published cases. They found a total of 61 cases from the first described case in 1939 to 2019. Most of the patients initially presented with increasing dyspnea. Many had the sensation of chest heaviness and also typical signs of hypocalcemia like Trousseau sign or Chovstek´s sign were documented. The clinical examination furthermore showed an elongation of the QT interval, left ventricular dilatation with reduced ejection fraction and edema in the lung and/or the feet. The data showed that the most common cause of hypocalcemic CMP was hypoparathyroidism (86 %) mainly linked to primary hypoparathyroidism (50 %) and only 26 % of the patients suffered from hypoparathyroidism after thyroidectomy. The theory behind this observation is that patients after anterior neck dissection are more closely controlled after surgery and therefore are more likely to be diagnosed. Patients with idiopathic hypoparathyroidism are prone to delayed diagnosis and consequently have a longer period of hypocalcemia before diagnosis (65).

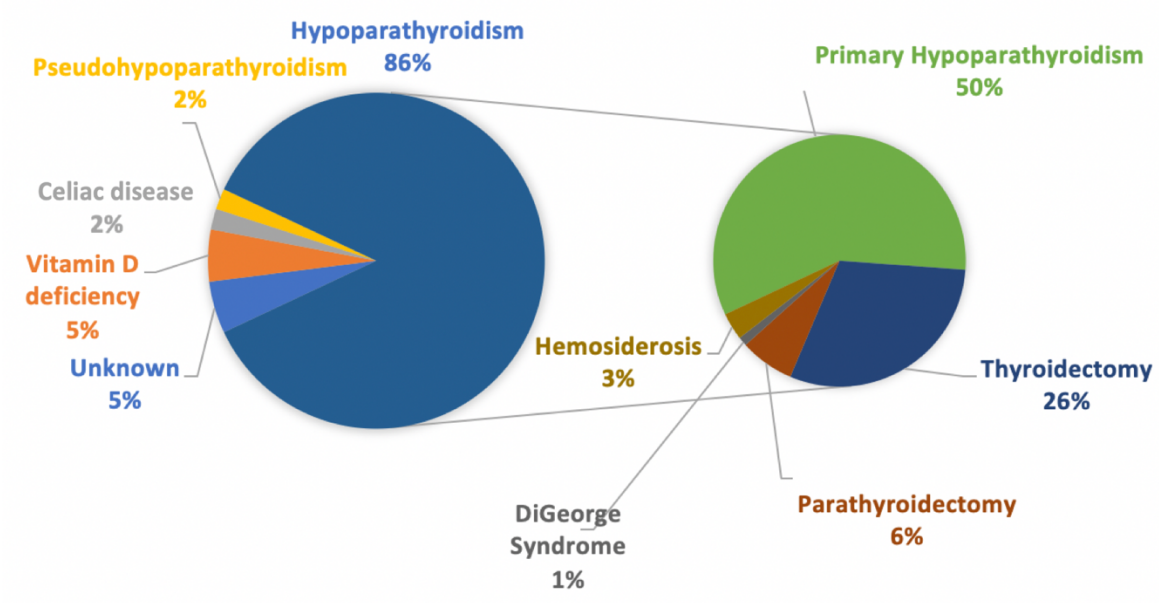

Figure 6: Different causes of hypocalcemic cardiomyopathy (modified with permission from Valek et al. 2020)

(65)

The cases were categorized by means of their cardiac ejection fraction into heart failure with reduced ejection fraction (HFrEF; EF < 40 %), heart failure with mid-range ejection fraction (HFmrEF; EF 40-49 %) and heart failure with preserved ejection fraction (EF ≥ 50 %). Of 39 cases with documented left ventricular ejection fraction (LVEF) 87 % suffered from HFrEF, 11 % were categorized as HFmrEF and one had preserved ejection fraction. Of the patients with HFrEF and HFmrEF 83 % showed diffuse left ventricular dysfunction and only in 10 % of the patients regional dyskinesis of the heart was reported. Besides heart failure, the patients also showed different forms of arrhythmia. Atrial fibrillation was documented in three patients, ventricular tachycardia in four, ventricular extrasystoles in one and junctional tachycardia in one. Interestingly, many patients also showed brain calcifications (n = 12), cataract (n = 12), cognitive dysfunction (n = 11), teeth destruction (n = 3) and hypocalcemic convulsions that were misdiagnosed as epilepsy (n = 4).

When no other explanation for the congestive heart failure was determined and the patients were treated for hypoparathyroidism, cardiac function improved or even normalized over time with rising serum calcium levels. This process took a differing length of time from months to years.

Of the reported cases, nearly 75 % regained normal left ventricular systolic function and 21 % at least hat a significant improvement of their LVEF. The few remaining patients did not regain left ventricular function. This might be due to poor compliance, degeneration of

myocytes or myocardial fibrosis (Válek *et al.*, 2020). A good example for the treatability of hypocalcemic CMP is the first case published by Bansal et al. in 2014. The serum calcium level of the described patient was not measured when the patient initially presented with an LVEF of 25 % on July 13, 2012. Consequently, the patient was then traditionally treated for heart failure with diuretics, digoxin, betablocker and an angiotensin-converting enzyme inhibitor. This treatment did not achieve the desired improvement. The patient suffered from dizziness, muscular spasms and general seizures resulting in another presentation three months later in October 2012. This time the hypocalcemia was detected and treated, resulting in a clear improvement of the symptoms and an EF increase from initially 24 % to 35 % until the first follow-up two weeks later. Another two months, later the patient was free of symptoms and the EF had returned to near normal with 52 % (64).

Table 12: Data and course of disease of a patient with severe hypocalcemic CMP

	July 13, 2012	*Oct 3, 2012*	*Oct 16, 2012*	*Dec 10, 2012*	*Jan 29, 2014*
Serum calcium (mg/dl)	-	3.5	8.2	13.5	8.9
LVEF (%)	25	-	35	56	52
Symptoms	weakness, progessive dyspnoe on excerion, bilateral lung crepitations, chest heaviness, paresthesia	episodic dizziness muscular spasms generalized seizures positive Trousseau sign pedal edema bilaterals lung crepitations	symptomatic improvement	asymptomatic	asymptomatic

(64)

Further literature research revealed 6 more cases of hypocalcemia associated cardiomyopathy between 2019 and 2022 (see Table 13). All of those cases showed similar symptoms to those described by Válek et al. in 2020. Interestingly in 2019 Anum Fasih published the first case of a patient with pseudohypoparathyroidism and cardiomyopathy. This indicates that also patients with pseudohypoparathyroidism can suffer from impaired cardiac function (66).

Table 13: Published cases of hypocalcemic cardiomyopathy from 2019 to 2022

Author	*Journal*	*Year*	*Age*	*Sex*	*Aetiology*	*ECG and EF*
Zhang 2020	J Int Med Res.	2020	62	male	Parathyroidectomy	Long QT, EF 27 %
Anum Fasih 2019	Eur J Case Rep Intern Med.	2019	22	male	Pseudohypoparathyroidism	EF 25 %
da Silva Santos 2022	Am J Emerg Med	2021	42	female	Thyroidectomy	Long QT, T-wave inversion in I, V1-3, EF 30 %
Tanabe 2021	Cureus.	2021	82	female	Thyroidectomy	Long QT, T-wave

						inversion in V3-6, EF 15 %
Wang 2021	World J Clin Cases.	2021	64	female	Thyroidectomy	Long QT, EF 28 %
Wen 2022	Frontiers in Cardiovascular Medicine	2022	58	female	Thyroidectomy	Long QT, EF 43 %

(66–71)

In 2014 Newman et al. analyzed the correlation of low serum calcium and cardiac abnormalities. The data of 47 patients who met the criteria was included. Of those patients, 37 (78 %) had reported heart failure and decreased LVEF was documented in 24 (51 %) of the 47 patients. They found a significant correlation between LVEF and corrected tCa ($B = 5.16$, $SE = 1.29$, $P < 0.01$) and between LVEF and iCa ($B = 5.48$, $SE = 2.04$, $P = 0.03$). This suggests that lower serum calcium concentrations may lead to worse cardiac function (72).

Besides being a possible cause of cardiomyopathy, hypocalcemia might also be a predictive marker for re-hospitalization or even mortality of heart failure patients without hypoparathyroidism. In 2020 Liu et al. analyzed the data of 350 patients suffering from heart failure with preserved ejection fraction (HFpEF). The patients were categorized depending on their serum calcium levels resulting in groups with hypocalcemia (below 1.18 mmol/L), normocalcemia (1.18 – 1.32 mmol/L) and hypercalcemia (above 1.32 mmol/L). They measured calcium levels, cardiac function, quality of life and six-minute walk test. The results showed that the risk of re-hospitalization during the follow-up period of 12 month was significantly increased in the patient-group with HFpEF and hypocalcemia compared to those with non-hypocalcemia (HR: 2.10, 95 % CI: 1.69-2.61). Also the risk of death during follow-up was substantially increased in hypocalcemic patients (HR: 8.26, 95 % CI: 2.88-23.70) (73).

Those results strengthen the data that was obtained in a study by Jensen et al. in 2019. In this study a total of 2729 patients with heart failure were included and split into groups of hypocalcemia (below 1.18 mmol/L), normocalcemia (1.18 - 1.32 mmol/L) and hypercalcemia (above 1.32 mmol/L). The results showed an increased mortality of hypocalcemic patients compared to those with normocalcemia during the 30 days short term

follow-up (HR: 2.22, 95 % CI: 1.74-2.82) and the long term follow-up between 31 and 90 days (HR: 1.52, 95 % CI: 1.12-2.05) (74).

3.1.3 Arterial stiffness and blood pressure

A Turkish study from 2019 analyzed the correlation between hypoparathyroidism and arterial stiffness and blood pressure. 42 patients with the diagnosis of nonsurgical or permanent postsurgical hypoparathyroidism were compared to 60 controls. Postsurgical hypoparathyroidism was defined as inadequately low PTH for 6 month or longer. Patients and controls were matched regarding the age, gender and body mass index (BMI). Patients and controls were excluded under following circumstances: age under 18 years, existing chronic disease, hypo- or hyperthyroidism, smoking, pregnancy and lactation. Of the included patients there were 22 (78.6 %) with permanent postsurgical hypoparathyroidism, 8 (19 %) with primary idiopathic hypoparathyroidism and 1 (2.4 %) with autoimmune polyglandular syndrome. Besides age, gender and BMI there was also no statistical difference in plasma glucose, serum creatinine, TSH, fT4, albumin, magnesium or 25-OH vitamin D levels between the compared groups.

For the measurement of the arterial stiffness, an oscillometric method was used at the brachial artery. After a 15-minute resting period for every participant, four measurements were performed with a 5-minute gap between each. Only very high-quality measurement data was included into the study. A series of different measurements were taken including, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), pulse pressure (PP), central systolic blood pressure (cSBP), central diastolic blood pressure (cDBP), central pulse pressure (cPP), augmentation pressure (AP), augmentation index corrected depending on 75 pulse/min (Aix@75) and pulse wave velocity (PWV).

The study shows a significant inverse correlation between the serum calcium levels and SBP, DBP, MAP, cSBP, cDBP, cPP and PWV. In contrast serum phosphorus levels correlated significantly positive with SBP, DBP, MAP, cSBP, cDBP, cPP and PWV. Furthermore, the serum levels of PTH had a significantly negative correlation with SBP, DBP, MAP, cSBP, cDBP, cPP and PWV. Since increased pulse wave velocity is a marker for arterial stiffness, the results of this study show a significant correlation between hypoparathyroidism, arterial blood pressure and arterial stiffness (75).

Table 14: Correlation of calcium, phosphorus, calcium-phosphorus-product and PTH with measurements for blood pressure and pulse wave velocity.

	Calcium (corr.)		***Phosphorus***		***Ca × P***		***PTH***	
	r	**p**	**r**	**p**	**r**	**p**	**r**	**p**
SBP (mmHg)	-0.29	0.003	0.287	0.004	0.249	0.01	-0.241	0.015
DBP (mmHg)	-0.285	0.004	0.254	0.01	0.203	0.04	-0.196	0.048
MAP (mmHg)	-0.296	0.003	0.279	0.005	0.231	0.02	-0.204	0.04
PP (mmHg)	NS	NS	NS	NS	NS	NS	NS	NS
cSBP (mmHg)	-0,365	<0.001	0.305	0.002	0.245	0.01	-0.283	0.004
cDBP (mmHg)	-0.253	0.01	0.239	0.02	NS	NS	NS	NS
cPP (mmHg)	-0.202	0.04	NS	NS	NS	NS	-0.203	0.04
AP (mmHg)	NS	NS	0.203	0.04	NS	NS	-0.203	0.04
Aix@75 (%)	NS	NS	NS	NS	NS	NS	NS	NS
PWV (m/s)	-0.243	0.01	0.269	0.006	0.256	0.009	NS	NS

(75)

In 2018, Underbjerg et al. specifically compared patients from the Danish cohort with nonsurgical hypoparathyroidism to patients with pseudohypoparathyroidism in terms of their cardiovascular profile and risk factors. 56 patients with nonsurgical hypoparathyroidism and 30 with pseudohypoparathyroidism were included into the study. Besides blood sampling also the blood pressure, pulse wave velocity and arterial stiffness were measured. Both groups were statistically similar in terms of prior cardiovascular disease, smoking, use of calcium or vitamin D supplementation and treatment with cholesterol-lowering or antihypertensive drugs. The group of patients diagnosed with nonsurgical hypoparathyroidism was significantly older ($P < 0.01$) and taller ($P < 0.01$) than the group diagnosed with pseudohypoparathyroidism. There was no significant difference in weight or BMI. Of the patients with nonsurgical hypoparathyroidism, 16 had autosomal dominant hypocalcemia (ADH), 7 had a 22q11 deletion and one had an AIRE mutation. Of the patients with 22q11 deletion, three already had had surgery due to congenital heart failure. The group of patients with pseudohypoparathyroidism consisted of 4 with type 1a/c, 2 with type 1b and 3 with pseudopseudohypoparathyroidism. In addition to the patients with pseudohypoparathyroidism 12 had hypothyroidism, 4 had abnormal gonadotropins and 1 had Addison's disease.

This study detected a significantly higher pulse wave velocity in patients with nonsurgical hypoparathyroidism compared to pseudohypoparathyroidism ($p = 0.02$) which did not change if adjusted for mean arterial pressure, body mass index, age, gender and plasma levels

of TSH and 25-hydroxyvitamin D. Furthermore, a significantly elevated heart rate in patients with nonsurgical hypoparathyroidism compared to those with pseudohypoparathyroidism was detected during 24-hour measurement ($p = 0.03$). Conversely, this difference could not be found when the heart rate was measured during office blood pressure measurement ($p = 0.90$). Blood pressure was not significantly different between the two groups (76).

Nonsurgical hypoparathyroidism has been associated with increased risk of cardiovascular events compared to the healthy population whereas this relation could not be shown for patients with pseudohypoparathyroidism (35,60). Therefore, the comparison of patients with nonsurgical hypoparathyroidism to those with pseudohypoparathyroidism in terms of cardiovascular risk factors might give an insight on why the risk of cardiovascular events is increased in those patients suffering from nonsurgical hypoparathyroidism. Since the only significant difference was a higher pulse wave velocity and increased heart rate in patients with nonsurgical hypoparathyroidism this could indicate that those are relevant factors for the increased risk of cardiovascular events (76).

As an explanation for the increased risk of calcifications it is assumed that a change in phosphate and calcium homeostasis favors the expression of bone and mineralization regulating factors in the wall of blood vessels. Therefore, an elevated serum PO_4 and an increased calcium phosphate product lead to mineralization of elastin components in the vessels (77). Interestingly an elevated phosphate concentration in the serum also increases the activity of Core-binding factor alpha1 (Cbfa-1) that provokes the transformation of smooth muscle cells into an osteoblastic phenotype (78).

3.1.4 Long QT syndrome and arrhythmia

Hypocalcemia is blamed for many manifestations of hypoparathyroidism including a prolongation of the QT-interval which is a predisposing factor for arrythmias with possibly life threatening consequences (58). The QT-interval is measured from the beginning of the QRS-complex to the end of the T-wave and is normally corrected (QTc) by Bazett´s formula ($QTc = QT/\sqrt{RR}$). The QTc-time should be below 440 ms in men and below 470 ms in women (79). A prolonged QT-interval can lead to cardiac arrythmia specifically torsade de pointes which is a dangerous form of polymorphic ventricular tachycardia. One of the causes of a long QT-time and following torsade de pointes are electrolyte abnormalities like hypocalcemia, hypokalemia and hypomagnesemia. Other causes are genetics, female gender, antiarrhythmic but also non-antiarrhythmic drugs and many more (80). Interestingly hypocalcemia leads to a QT-prolongation but only in rare cases does it trigger torsades de pointes tachycardia or other life-threatening forms of arrhythmia (81).

A study from Beijing published in 2020 compared 18 patients with hypoparathyroidism and 8 diagnosed with pseudohypoparathyroidism to 26 healthy individuals with no parathyroid or thyroid dysfunction, CVD or associated risk factors. The two groups were matched by age and sex. All patients received calcium and vitamin D as treatment. A 12-lead ECG was done in 19 of the 26 cases. The obtained data of those patients showed that 8 out of 14 individuals with hypoparathyroidism and 2 out of the 5 patients with pseudohypoparathyroidism had prolonged QTc-intervals. 473.0 ± 20.3 ms in patients with hypoparathyroidism (Table 15) and 455.5 ± 6.4 ms in patients with pseudohypoparathyroidism. No significant morphological changes of the left ventricle or changes in the left ventricular systolic function were detected. The left ventricular ejection fraction (LVEF) was not significantly different between patients with hypoparathyroidism and controls, neither was the difference between patients diagnosed with pseudohypoparathyroidism and controls (82).
In comparison Newman et al. did a systematic review and meta-analyses of available patient data. They found and analyzed a total of 47 cases that showed hypocalcemia and documentation of cardiac dysfunction. Of the 47 cases 39 (83 %) had primary or secondary hypoparathyroidism. Cases with further diseases that could interfere with cardiac function were excluded. In 18 of the included 47 cases (38 %), a prolonged QT-interval was documented with a median QTc of 510 ms and a total range of 350 to 700 ms. Furthermore,

they found a statistically significant correlation of the QTc-time and corrected tCa (B = -23.19, SE = 8.04, P = 0.01), between LVEF and corrected tCa (B = 5.16, SE = 1.29, P < 0.01) and between LVEF and iCa (B = 5.48, SE = 2.04, P = 0.03). Interestingly, the cardiac manifestations were reversible under treatment in 46 out of 47 patients (98 %). This shows a strong correlation between calcium and QTc-time but it has a risk for bias since patient data was partly incomplete and further diseases that might affect the cardiovascular system could not be excluded in many cases (72).

A difference between the studies of Newman et al. and Wang et al. might be that the patients of the second study already received a therapy with calcium and vitamin D. Therefore, the patients with hypoparathyroidism in the study of Wang et al. had a mean serum calcium of 2.05 ±0.16 mmol/l whereas the mean tCa of the patients analyzed by Newman et al. was 1.18 (0.53-2.05) mmol/l. This might further suggest that the prolonged QT-interval correlates with the serum calcium and not the serum levels of parathyroid hormone (see Table 15).

Table 15: Comparison of the data for QTc time and tCa in two studies

	QTc	*tCa*
Wang 2020	473.0 ± 20.3 ms	2.05 ±0.16 mmol/l
Newman 2014	510 ms (350 – 700)	1.18 (0.53-2.05) mmol/l

(72,82)

3.1.5 Influence of hypoparathyroidism therapy on the cardiovascular system

A recent study from 2022 compared 113 patients with chronic hypoparathyroidism under treatment with rhPTH(1-84) to a control group of 618 individuals that received a conventional treatment. The mean age of controls was significantly higher. Additionally, potential risk factors like arterial hypertension, diabetes and dyslipidemia occurred significantly more often. Over the observation period of 5 years, only 3.5 % (n = 4) of the patients receiving rhPTH(1-84) suffered a cardiovascular event. 1 had coronary artery disease, 1 suffered from cerebrovascular disease, 2 patients were diagnosed with heart failure and 1 with peripheral vascular disease. On the other hand, a total of 16.3 % (n = 101) controls had a cardiovascular event during the observational time. Of those individuals 32 (31.7 %) suffered from cerebrovascular disease, 33 (32.7 %) had a form of coronary artery disease, 21 (20.8 %) were diagnosed with heart failure and 22 (21.8 %) with peripheral vascular disease. This shows that under treatment with rhPTH(1-84) the cardiovascular risk may be significantly lower than with conventional therapy (P = 0.005) (83).

One risk factor under the treatment of hypoparathyroidism is temporary (treatment-related iatrogenic) hypercalcemia. Depending on the number of hypercalcemic events, the risk of CVD is increased. For patients with a history of four or more hypercalcemic events, the risk of CVD is significantly elevated compared to patients without any events (OR_{adj} 9.69; 95 % CI, 2.63-35.79) (84). A study from 2013 suggested that the therapy of hypoparathyroidism with calcium has no negative effect on the risk of cardiovascular disease compared to the general background population. It can be argued that in therapy of hypoparathyroidism, as the desired calcium levels are in the low normal range, the risk for transient hypercalcemia is low (34).

3.2 Neurological manifestations of hypoparathyroidism

The symptoms of hypoparathyroidism are mainly linked to the lack of calcium but also the dysbalanced homeostasis of other minerals like phosphate or magnesium play an important role in the manifestation of the different symptoms of patients with hypoparathyroidism. An impairment of brain function due to hypoparathyroidism might result in altered neurological and cognitive capacities (32). The different neurological, neuromuscular and neuropsychiatric manifestations linked to hypoparathyroidism are listed in the following table (see Table 16).

Table 16: Neuromuscular, neurological and neuropsychiatric manifestations of hypoparathyroidism

Neuromuscular manifestations	Tetany Muscle cramping (carpal/pedal spasms) Twitching (Chovstek´s sign, Trousseau´s sign) Laryngospasm, stridor, bronchospasm and wheezing Fatigue Muscle weakness Muscle pain Heaviness in extremities Prolonged muscular recovery after exertion
Neurological manifestations	Involvement of the CNS: • Impaired neurocognitive function including impaired memory and concentration • seizures • basal ganglia and brain calcifications • parkinsonism/dystonia • altered mental status • pseudotumor cerebri • extrapyramidal disorders • chorea Involvement of the PNS: • paresthesia and numbness (acral and perioral)
Neuropsychiatric manifestations	Depression Anxiety Personality disturbances

(37)

3.2.1 Manifestations of the peripheral nervous system

Hypocalcemia interferes with the physiological depolarization of neurons. The manifestations can be divided into those caused by increased irritability of sensory neurons and those caused by motor neurons. Paresthesia in the peri-oral region or in the extremities is linked to the sensory neurons. Muscle spasms or tetany are caused by the more easily depolarized sensory neurons. Since the spasms can reach from light twitching of the forearm, hand and distal leg called carpopedal spasms to laryngospasms which have to be considered as life-threatening it is important to recognize the clinical signs as soon as possible and evaluate the possibility of hypocalcemia as cause of stridor or even apnea without clear trigger (37,38). To help with the detection of increased motor neuron irritability, Chvostek sign and Trousseau signs are used (37).

3.2.2 Neuromuscular manifestations and seizures

The prevalence of central neuromuscular complications in association with hypoparathyroidism is reported to be between 4 to 12 %. The most common presentation of symptoms is parkinsonism with a combination of bradykinesia, mask-like faces, resting tremor, and mixing posture). Less common is the presentation of patients with extrapyramidal signs like choreiform movements, hemiballismus or signs of cerebellar involvement like ataxia or dysarthria (85).

Seizures can be provoked by low levels of calcium in the serum. The clinical manifestation can reach from focal or generalized seizures (tonic-clonic type) (37). Different studies analyzed the prevalence of seizures in patients with hypoparathyroidism (see Table 17). In a study from 2015 Underbjerg et al. compared the rate of different complications of nonsurgical hypoparathyroidism to a healthy control population. They found that the risk of seizures was 10 times higher for patients than controls (HR 10.05; 5 % CI, 5.39-18.72) (35). Two years earlier in 2013 Underbjerg and colleagues already did a similar comparison between patients with postsurgical hypoparathyroidism and healthy controls. The results also showed an significantly increased risk of seizures for patients (34). Finally, also patients suffering from pseudohypoparathyroidism have a significantly increased risk of seizures compared to the healthy population (60). Mitchell et al. analyzed a cohort consisting of a total of 120 patients with permanent hypoparathyroidism. Of the 107 patients with acquired

hypoparathyroidism, 79 had postsurgical, 9 autoimmune and 19 idiopathic acquired hypoparathyroidism. Furthermore, 13 patients were born with hypoparathyroidism which was caused by activating CaSR mutation in 5, DiGeorge syndrome in 3, Kearns-Sayre syndrome in 1 patient and 4 suffered from idiopathic congenital hypoparathyroidism. Seizures were reported in 10 (8 %) of the patients and of those 8 had already started therapy at the time of the seizure (86).

Table 17: Rate of seizures in nonsurgical-, postsurgical- and pseudo hypoparathyroidism

Study	*disease*	*patients*	*controls*	*HR*	*95 % CI*
Underbjerg 2015	ns-hypoPT	42 (23.3 %)	13 (2.4 %)	10.05	5.39-18.72
Underbjerg 2013	ps-hypoPT	26 (3.8 %)	21 (1.0 %)	3.82	2.15-6.79
Underbjerg 2016	pseudo-hypoPT	10 (16.6 %)	6 (3.3 %)	5.53	1.94-14.74

(34,35,60)

3.2.3 Basal ganglia calcification

The term “basal ganglia” usually refers to the globus pallidus and the striatum, consisting of the caudate nucleus and the putamen. Both are nuclei located in the brain hemispheres. Often the definition is extended to include functionally related nuclei in other locations like the subthalamic nucleus located in the diencephalon, the substantia nigra found in the mesencephalon and the pedunculopontine nucleus in the pons. The main task of those structures is motor control but also the engagement in motor learning, executive functions, behavior and emotions is reported (87). The abnormal deposition of calcium in the basal ganglia caused by various diseases is called Fahr´s syndrome. It has been suggested that the term Fahr´s syndrome should be distinguished from Fahr´s disease which is a rare hereditary neurodegenerative disease causing basal ganglia calcification. Symptoms are similar in both but etiology, treatment and prognosis of Fahr´s syndrome differ greatly from those of Fahr´s disease (88).

Over time different terms have been used to describe this condition. It is also referred to as “bilateral striopallidodentate calcinosis” (BSPDC) picturing the often bilaterally occurring calcifications with the basal ganglia and the caudate nucleus as preferred sites. Furthermore the term “idiopathic basal ganglia calcification” (IBGC) is used for familial cases of basal ganglia calcification (89).

Calcifications especially target areas that control movement involving striatum, pallidum, dentate nucleus, thalamus and white matter. The syndrome is mostly caused by

hypoparathyroidism but also pseudohypoparathyroidism, pseudo-pseudo-hypoparathyroidism and other diseases (88,90). Typical clinical manifestations include neuropsychiatric abnormalities and motor disorders (91).

3.2.3.1 Epidemiology

The frequency of basal ganglia calcification (BGC) in the general population is not well determined and has been reported to be between 0.2 % and 22.1 % in different studies (see Table 18). In the eighties, several studies analyzed the incidence of basal ganglia calcification. A study from 1982 reviewed 7120 CT scans and found 17 (0.24 %) with bilateral basal ganglia calcification (92). Kazis et al. analyzed 7040 CT scans, including patient with hypoparathyroidism and found 72 (1.02 %) showing symmetrical intracranial calcification (93). Another study examined 5000 CT brain scans and found 32 individuals with calcification (0.6 %). Since there were no correlating symptoms, they were classified as physiological calcifications. The rate of calcifications increased with age and only one case with calcification was found with an age below 40 (94).

More recent studies calculated a higher incidence which might be due to different diagnostic standards or the changed usage of CT-scans over the years (95). A study from 2001 detected basal ganglia calcification with an incidence of 12.5 % under a total of 2318 scans (96). Furthermore a Swedish study analyzed the cranial CT scans of the elderly population and found bilateral calcification in 254 individuals (22.1 %) out of 657 participants (97).

Table 18: Incidence of basal ganglia calcification in the general population

Study	*study population*	*Incidence*
Selekler 1982	7120	0.24 %
Kazis 1985	7040	1.02 %
Cohen 1980	5000	0.6 %
Gomille 2001	2318	12.5 %
Simoni 2008	657	22.1 %

(92–94,96,97)

A study from Denmark tried to determine the prevalence of basal ganglia calcification in patients with hypoparathyroidism. The results showed that 11 out of 16 patients (69 %) with idiopathic hypoparathyroidism and all of the eight patients with pseudohypoparathyroidism were diagnosed with basal ganglia calcification. (98).

Goswami *et al.* included 145 patients with idiopathic hypoparathyroidism. In 73.8 % of those cases, basal ganglia calcification was diagnosed (99).

A small study included a total of 11 patients. Out of the 9 with postsurgical hypoparathyroidism, 5 had calcification of the basal ganglia. Both patients with primary hypoparathyroidism had abnormal calcifications of the basal ganglia (100). Another study compared the risk of basal ganglia calcification in 29 patients with permanent postsurgical hypoparathyroidism to a control group of 501 patients. In six of the patients with hypoparathyroidism, a calcification of the basal ganglia was diagnosed (20.7 %). This is the equivalent of a four times higher risk for patients with hypoparathyroidism compared to controls after propensity score matching (101). Zavatta et al. analyzed the data of 142 patients diagnosed with chronic hypoparathyroidism and compared them to 426 controls matched by age and sex. Of the patients, 25.4 % had basal ganglia calcification which results in a 5.1-times higher risk of basal ganglia calcification in patients with chronic hypoparathyroidism compared to healthy controls (102).

Table 19: Rate of basal ganglia calcification in patients with different forms of hypoparathyroidism

Study	*idiopathic hypoparathyroidism*	*postsurgical hypoparathyroidism*	*pseudohypoparathyroidism*
Illum 1985	11/16 (69 %)	-	8/8 (100 %)
Goswami 2012	107/145 (73.8 %)	-	-
FORMAN 1980	-	5/9 (56 %)	-
Lorente-Poch 2020	-	6/29 (20.7 %)	-

(98–101)

Of the patients with BGC included in the study by Zavatta et al. 96 % had calcification located in the globus pallidus, 53.8 % in the putamen and caudate nucleus, 42.3 % in the thalamus, 46 % in the grey-white matter junction, 30.8 % in the cerebellum and 18.2 % in the dentate nucleus (102). Goswami and colleagues also analyzed the exact location of the calcifications in 107 patients with idiopathic hypoparathyroidism. Affected were the globus pallidus (68.8 %), putamen (55.9 %), caudate nucleus (54.8 %), grey white junction (39.8 %), cerebellum (31.2 %), thalamus (29.0 %) and dentate nuclei (24.7 %) (99).

Table 20: Location of basal ganglia calcification associated with hypoparathyroidism.

study	*globus pallidus*	*putamen*	*caudate nucleus*	*grey white junction*	*cerebellum*	*thalamus*	*dentate nucelei*
Zavatta 2020	96 %	53.8 %	53.8 %	46 %	30.8 %	42.3 %	18.2 %
Goswami 2012	68.8 %	55.9 %	54.8 %	39.8 %	31.2 %	29.0 %	24.5 %

(99,102)

The reason why the calcifications occur more frequently in patients with hypoparathyroidism or why exactly those areas of the brain are affected is not clear. It is argued that the concentration of phosphorus and calcium in the corticospinal fluid (CSF) might play an important role since in hypoparathyroidism the calcium levels of the CSF should stay constant even if in a hypocalcemic state (103) while the concentration of phosphorus in the CSF is increased (104,105). This results in an elevated calcium-phosphorus product in the CSF which might provoke pathological depositions especially in the periventricular regions (99). A further possibility would be metabolic or inflammatory processes that lead to calcification and ultimately neurological impairment (106). Also, three cases were reported that described patients who had suffered a meningoencephalitis in childhood and later developed basal ganglia calcification in the presence of a disturbed calcium homeostasis. This further more suggests a correlation between existing damage caused by inflammatory processes and the calcification found in the brains of the patients (107).

A study by Zavatta et al. determined that low serum calcium and low calcium/phosphate ratio are associated with basal ganglia calcification but neither phosphorus nor calcium-phosphate-product have an statistically significant influence on rate of calcification (102). That assumption is supported and extended by Goswami *et al.* who linked the manifestation and the progression of BGC to a low calcium/phosphorus ratio. This study furthermore showed that the basal ganglia calcification in patients with idiopathic hypoparathyroidism is a progressive manifestation associated with a long duration of hypoparathyroidism. This implies that a long-lasting hypoparathyroidism with symptomatic hypocalcemia and low calcium/phosphorus ratio might be risk factors promoting the occurrence of BGC (99). The connection between disease duration and prevalence of BGC is also encouraged by comparison of a study by Sachs, Sjörg and Ericson from 1982 which reported a prevalence of 93 % in patients with a mean duration of hypoparathyroidism of 19 years to one of

Goswami et al. from 2012 who found a prevalence of 73.8 % in 145 patients with a mean duration of hypocalcemic symptoms of 7.4 years (99,108). On the other hand, it is questionable if the data of those two studies is comparable due to the different diagnostic standards and possibilities at the time.

Table 21: Prevalence of basal ganglia calcification and mean disease duration

study	*prevalence of BGC*	*mean disease duration*
Sachs 1982	93 %	19 years
Goswami 2012	73.8 %	7.4 years

(99,108)

Several other mechanisms are suspected to play a part in the calcification of the basal ganglia in patients with hypoparathyroidism. Hyperphosphatemia might work in a similar way like uremia which causes smooth muscle calcification through activation of the bone transcription factor called runt related factor-2 (Runx2). Recent studies suggest the expression of this factor in the human brain (109). Hyperphosphatemia induces an upregulation of Runx2 in vascular smooth muscle fibers which has been linked to calcification. Furthermore, PTH seems to play a direct role in basal ganglia calcification (110).

PTH stimulates the adenylate cyclase that works as catalyst to turn adenosine triphosphate (ATP) into cyclic adenosine monophosphate (cAMP). The cAMP is then used as second messenger to stimulate further cellular pathways (111). A study measured the concentration of cAMP in the CSF after PTH administration. The values of a patient with strio-pallido-dentate calcinosis (SPDC) were compared to three healthy adults. The data showed a significantly decreased cAMP response in the patient (112). Also, there are PTH2 and PTH/PTHrp receptors present in the cerebellum and the basal ganglia. A study showed that PTH causes elevated calcium transport in cultured striatum cells of rats (113). Furthermore, PTH might affect the carbonic anhydrase 2 (114) that is found throughout the human body but is also located in the brain. Defects of this enzyme are known to cause cerebral calcifications (115).

3.2.3.2 Symptoms

Patients with calcification of the basal ganglia may present with different symptoms. A study included 99 cases of Fahr´s disease. 67 patients were symptomatic, with a higher incidence

among men. 55 % of the symptomatic cases suffered from a movement disorder. Of those, 57 % comprised of parkinsonism, 19 % chorea, 8 % tremor, 8 % dystonia, 5 % athetosis and 3 % orofacial dyskinesia. Furthermore, patients also suffered from other neurological symptoms like cognitive impairment, cerebellar signs, speech disorder, pyramidal signs, psychiatric features, gait disorders, sensory changes and pain.
The extent of the calcification was documented and showed a plausible correlation of the likelihood of more severe symptoms in patients with higher amounts of calcification (116). Data from a study analyzing 22 patients with Fahr´s syndrome supports the assumption that the extent of the calcification correlates with the manifestation of symptoms (106).
On the other hand Kazis et al. found no correlation between the extent of the calcification and neurological manifestations. Of the patients with extensive calcium deposition, 35.5 % suffered from neurological impairment compared to 34.5 % out of the cases with limited calcification of the basal ganglia (93). A study by Zavatta et al. also did not find an increased risk of neurological complications for patients with basal ganglia calcification (102).

Kalampokini *et al.* reviewed 223 cases of Fahr´s syndrome caused by hypoparathyroidism. The collective consisted of 39 % with idiopathic hypoparathyroidism, 35.4 % with acquired hypoparathyroidism and 25.6 % with pseudo hypoparathyroidism. Nearly half of those patients suffered from tetany, seizures or a movement disorder und around 40 % had neuropsychiatric symptoms. Patients suffering from a movement disorder also had a significantly higher risk of suffering from neuropsychiatric symptoms (OR 2.23, 95 % CI, 1.29-3.87) (117).

The location of calcium deposition correlates with the neurological manifestations. Though it seems like the correlation is stronger in T2-weighted sequences compared to CT scans. In a study 15 patients with Fahr´s syndrome presented with dementia and hyperintense white matter of the entire centrum semiovale in both brain hemispheres. Furthermore three patients that presented with hemiparesis and accordingly showed hyperintense sections of the contralateral internal capsule (106).

As a consequence of the extensive calcification patients may be at risk of suffering from intracerebral bleeding. This suggests a case report from Michigan, describing a 37-year old patient with idiopathic hypoparathyroidism, bilateral symmetrical calcifications of the basal ganglia, dentate nucleus, cerebellum and dentate nucleus (118).

3.2.3.3 Diagnosis

For the detection and further evaluation of the extent of the cerebral calcification computed tomography (CT) is preferred. On CT the depositions appear as hyperdense lesions which is considered essential for accurate diagnosis (119).

Also, plain skull radiography can be used to detect mineral depositions in the brain, but already in 1979 the a superiority for diagnosis using CT brain scan was demonstrated when out of 40 patients with basal ganglia calcification diagnosed with CT brain scan only in four the depositions were also visible in plain skull radiography (120).

The diagnosis with magnetic resonance imaging (MRI) is more complicated and studies differ on how to interpret the data correctly (121). In the MRI calcium depositions may appear bright on the T1 image, though the intensity of the signal decreases with higher concentrations. In the T2 plain calcification of the basal ganglia might present as hypointense/hyperintense. This is due to other minerals in the structure of the calcified areas such as Zinc, manganese, iron and magnesium. Moreover hyperintense T2-weighted regions may be a sign of an inflammation which could be causing the calcification but also might be consequence of it (89,119).

Further diagnosis of the calcification can be done with fluorodeoxyglucose positron emission tomography (FDG-PET) showing the level of metabolism in the given region. It is speculated that extensive calcification and hypometabolism are more likely to be found in symptomatic patients (122).

To differ between physiological age-related calcifications and pathological depositions it is important to watch for a few features. Physiological lesions are not accompanied by any disease or pathological manifestation. Furthermore, they are often small, symmetrical and focused on the globus pallidus. Pathological lesions are often more widespread and diffuse also involving the putamen and the dentate nucleus (89,123).

3.2.3.4 Treatment

A study analyzed the FDG-PET of a patient with idiopathic hypoparathyroidism and proximal kinesigenic choreoathetosis. The patients showed bilateral hypometabolism of the

striatum especially in the inferior part of the caudate nucleus and the putamen, in the FDG-PET before treatment. Additionally, calcification of the basal ganglia was found. After one year of treatment with calcitriol and calcium supplementations, the metabolism had normalized, and the patient was asymptomatic. Calcifications did not regress (124).

3.2.4 Neuropsychiatric manifestations

Besides a variety of other complications, many patients suffering from hypoparathyroidism commonly report problems to concentrate often described as “brain fog” (36,125).

To compare the neurological and neuropsychological functions of patients with idiopathic hypoparathyroidism to those of healthy individuals a study by Aggarwal and colleagues assessed 62 patients and 70 healthy controls in terms of their cognitive capabilities. The results showed a significant difference with 32.3 % (95 % CI: 20.9-45.3) of the patients and only 5.7 % (95 % CI: 1.6-14.0) of the healthy individuals suffering from neuropsychological dysfunctions. Neurological symptoms were documented for 35.5 % of the patients (16.1 % extrapyramidal and 20.9 % cerebellar). Thereby the volume or number of basal ganglia calcification did not correlate with the manifestation of neurological or neuropsychological dysfunction. The results suggest that the cognitive dysfunction correlates with male gender ($p = 0.02$) and also increases with longer duration of the illness ($p = 0.001$) as well as the elevated serum calcium-phosphorus product ($p = 0.01$). Higher serum calcium was associated with lower cognitive dysfunction (126).

Sardella et al. collected the existing case reports on patients with hypoparathyroidism associated with impaired cognitive capabilities. They included a total of 17 cases into their review. The analyzation of the cases suggests a common association between hypoparathyroidism and neuropsychological problems. In the case reports cognitive impairments like confusion, attention deficits, reduced inhibitory control and psychomotor retardation were reported (127).

A study from 2002 furthermore found that patients suffering from hypoparathyroidism under treatment with calcium still suffer from phobic anxiety and anxiety more often than controls with intact PTH production (128). Cusano et al. also found an impaired quality of life reported by patients diagnosed with hypoparathyroidism. Under treatment with PTH (1-84) the scores checking for reduced QOL including mental health improved significantly suggesting a neuropsychiatric benefit for patients treated with hormone substitution (129).

4 Discussion

Cardiovascular manifestations

The collected information in this thesis shows that the risk of cardiovascular risk differs for patients with different forms of hypoparathyroidism. The risk of any cardiovascular complication (HR 1.91; 95 % CI, 1.29-2.81) including ischemic heart disease (HR 2.01; 95 % CI, 2.01-3.09), stroke (HR 1.84; 95 % CI, 0.5-3.54) and arrhythmia (HR 1.78; 95 % CI, 0.96-3.30) is significantly increased for patients with nonsurgical hypoparathyroidism whereas the there is no significantly higher risk for patients with postsurgical hypoparathyroidism (when adjusted for preexisting cardiovascular disease) nor is the risk increased for patients with pseudo- and pseudopseudohypoparathyroidism (34,35,60). This might be due to the longer time until diagnosis/treatment. Postsurgical hypoparathyroidism is often diagnosed rather rapidly after the surgical intervention. Therefore, the disbalance of PTH, calcium and phosphate with all its consequences is more likely to persist over a longer period of time in patients with nonsurgical hypoparathyroidism than in those with a postsurgical etiology. More studies are necessary to determine the exact reason of increased cardiovascular risk for patients with nonsurgical hypoparathyroidism and potential strategies to mitigate this risk.

Patients with postsurgical hypoparathyroidism are more likely to suffer from cardiovascular autonomic neuropathy (61) which is also linked to increased fatigue, a problem known to occur often in postsurgical hypoparathyroidism (63). Interestingly, CAN also correlates with disease duration and lower concentrations of calcium (61). At the time of writing, the two publications of Tabacco et al. are the only ones that focus on this topic. Therefore, more work in this direction would be necessary to determine the detailed impact on the quality of life, fatigue or other problems that accompany autonomic cardiovascular neuropathy like increased mortality of cardiac arrhythmias.

Hypocalcemia is a treatable cause of dilated cardiomyopathy and hypoparathyroidism is the most common cause of a hypocalcemic state in this context (64). Patients present with increasing dyspnea and chest heaviness with typical signs of hypocalcemia like positive Trousseau sign and/or Chovstek´s sign. Furthermore, the QT interval is often prolonged. The impaired ejection fraction is often not treatable with traditional heart failure therapy but recovers under adequate therapy of hypocalcemia when normal calcium levels are restored

over weeks and months (65). The left ventricular ejection fraction correlates with low calcium levels (72). Furthermore, hypocalcemia also is a predicting factor for patients with heart failure not caused by hypoparathyroidism. The rate of re-hospitalization was increased for patients with HFpEF and low calcium levels (73). Furthermore, it is suggested that the mortality of patients with hypocalcemia and heart failure is significantly increased (73,74). Cardiomyopathy and the accompanying signs of heart failure are a rare complication of hypoparathyroidism. Literature research revealed 67 cases of CMP linked to hypoparathyroidism documented in the available English literature in the time from 1939 to 2022 (65–71), but it can be assumed that the true number is substantially higher. Therefore, hypocalcemia should be excluded when the cause of CMP is unclear.

Nonsurgical and permanent postsurgical hypoparathyroidism are associated with increased pulse wave velocity (75). Furthermore, compared to patients with pseudohypoparathyroidism the pulse wave velocity and heart rate are significantly higher in patients with nonsurgical hypoparathyroidism (76). Since the risk of cardiovascular events is only increased in patients with nonsurgical hypoparathyroidism and not pseudohypoparathyroidism (35,60) the two factors of pulse wave velocity and heart rate might be an important trigger or at least indicating factor for increased cardiovascular risk (76). Furthermore the laboratory data of calcium, phosphorus and the calcium phosphate product correlate significantly with the pulse wave velocity (75) - which suggests that undertreatment of hypoparathyroidism increases the risk of cardiovascular complications.

A significant inverse correlation between the QT-interval and serum calcium concentration has been reported. Since a prolonged QT-time is known to increase the risk of arrhythmia also a correlation of low serum calcium and arrhythmia can be assumed (58,72).

A recent study using historical controls reported a higher rate of cardiovascular complications (16.3 %) in hypoparathyroid patients under traditional treatment as opposed to only 3.5 % treated with rhPTH(1-84), however the control group was significantly older and had a higher prevalence of traditional cardiovascular risk factors, therefore these findings must be interpreted with caution (83).

Neurological manifestations

Seizures occurred significantly more often in patients with hypoparathyroidism compared to healthy controls. This includes all forms of hypoparathyroidism. Patients with nonsurgical hypoparathyroidism seem to be at the highest risk, whereas those with postsurgical hypoparathyroidism have the lowest risk of suffering a seizure (34,35,60).

The incidence of basal ganglia calcifications is documented to be between 0.2 to 22.1 % in the general population (92–94,96,97). This might depend on the exact composition of the study population or the diagnostic standards and the quality of imaging techniques.
On the other hand, it is suggested in the literature that 69 % to 74 % of the patients with nonsurgical hypoparathyroidism suffer from basal ganglia calcification (98,99) and 21 % to 56 % of patients with postsurgical hypoparathyroidism (100,101). The manifestation of the calcifications could be linked to a low serum calcium and a low calcium/phosphate ratio (102). The association between basal ganglia calcification and a low calcium/phosphorus ratio is supported by Goswami et al. who also suggested a connection between the progression of the calcifications and calcium/phosphorus ratio and additionally to the duration of the hypoparathyroidism (99). In terms of association between basal ganglia calcification and neurological symptoms, there are different suggestions to be found in the available literature. Two studies from 1994 and 2001 support the assumption that the extention of the calcification correlates with the manifestation of neurological symptoms (106,130). On the other hand, Kazis et al., Zavatta et al. and Aggarwal et al. found no association of the extent or the existence of basal ganglia calcification and the manifestation of neurological symptoms (93,102,126). In 2001, a study reported that the metabolism of the affected areas and the symptoms of the patients regressed under treatment but the calcifications themselves did not (124). The association of hypoparathyroidism and basal ganglia calcification is represented throughout the literature. However, the connection between basal ganglia calcification and neurological manifestations of patients with hypoparathyroidism is less clear. This implies that hypocalcemia can cause a change of brain function with visible changes. Therefore, if basal ganglia calcification due to unknown origin is diagnosed in a patient it might be reasonable to consider the presence of hypoparathyroidism as cause. More sophisticated analyses including functional MRI studies will shed more light on these topics in the future.

It has been documented that patients suffering from hypoparathyroidism have impaired neuropsychological function in comparison to healthy individuals. The decreased cognitive functions correlate with male gender, duration of hypoparathyroidism and serum calcium-phosphorus product (126,127). More work in this direction is necessary to determine the concrete cause and the correlations of impaired cognitive function. Again, disease duration appears to be an important risk factor.

Interpretation

This thesis shows that cardiovascular and neurological complications of hypoparathyroidism should be considered in everyday clinical life. If patients present with signs of heart failure, arrhythmia, arterial stiffness or cardiovascular autonomic neuropathy in combination with typical signs of hypoparathyroidism like paresthesia, Chvostek's sign, Trousseau sign or a typical patient history with neck surgery, hypoparathyroidism should be considered. Also impaired cognitive function and neuromuscular complications like parkinsonism or spasms should be considered as possible manifestations of hypoparathyroidism and treated accordingly.

A common factor correlating with the complications of hypoparathyroidism like different neurological manifestations but also heart failure is the untreated duration of hypoparathyroidism. Therefore, a prompt diagnosis and adequate treatment appear to be important.

Limitations and recommendations

Cardiovascular and neurological manifestations of hypoparathyroidism are rare and data is limited, but due to the good treatability of most cases of hypoparathyroidism they should be diagnosed correctly. Concerning the hormone replacement therapy there is more work to be done assessing the long-term cardiovascular and neurological benefits.

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6 Attachment

Laienzusammenfassung

Der Hypoparathyreoidismus ist eine seltene Erkrankung bei der es zu einem Missverhältnis zwischen dem Nebenschilddrüsenhormon (PTH) und den Mineralstoffen, wie Kalzium und Phosphat kommt, welche durch PTH gesteuert werden. Dies hat eine Reihe an Auswirkungen, wie beispielsweise Missempfindungen und Krämpfe. In manchen Fällen wurde jedoch auch das Auftreten von kardiovaskulären Auswirkungen, wie Rhythmusstörungen oder eine eingeschränkte Pumpleistung des Herzens beschrieben. Auch neurologische Auswirkungen im Sinne von Krampfanfällen oder eingeschränkter Kognition wurden bereits dokumentiert.

Diese Arbeit befasst sich speziell mit in der bestehenden Literatur bereits dokumentierten kardiovaskulären und neurologischen Auswirkungen des Hypoparathyreoidismus.

Die Auswertung der vorliegenden Literatur zeigt, dass Hypoparathyreoidismus und speziell der damit einhergehende Mangel an Kalzium zu einer Verlängerung des QT-Intervalls und damit zu Rhythmusstörungen führen kann. Diese Anzeichen sind wichtig zu erkennen, da es sich oft um behandelbare Auswirkung des gestörten Mineralstoffhaushaltes handelt. Dabei gibt es Hinweise, dass eine Therapie mittels Hormonsubstitution ein besseres Ergebnis in Bezug auf Störungen des Herz-Kreislauf-Systems erreichen könnte. Die Studienergebnisse sind allerdings nicht eindeutig interpretierbar.

Bezogen auf neurologische Auswirkungen von Hypoparathyreoidismus ist auffällig, dass es gehäuft zu Verkalkung der Basalganglien im Gehirn kommt. Diese Strukturen sind wichtig für die Kontrolle von Bewegungen. Somit werden Basalganglienverkalkungen mit Symptomen, wie Bewegungsstörungen in Verbindung gebracht. Ein eindeutiger Zusammenhang konnte jedoch noch nicht bewiesen werden. Weiters kann es im Zusammenhang mit Hypoparathyreoidismus zur Einschränkung der neurokognitiven Leistungsfähigkeit sowie der Lebensqualität kommen.