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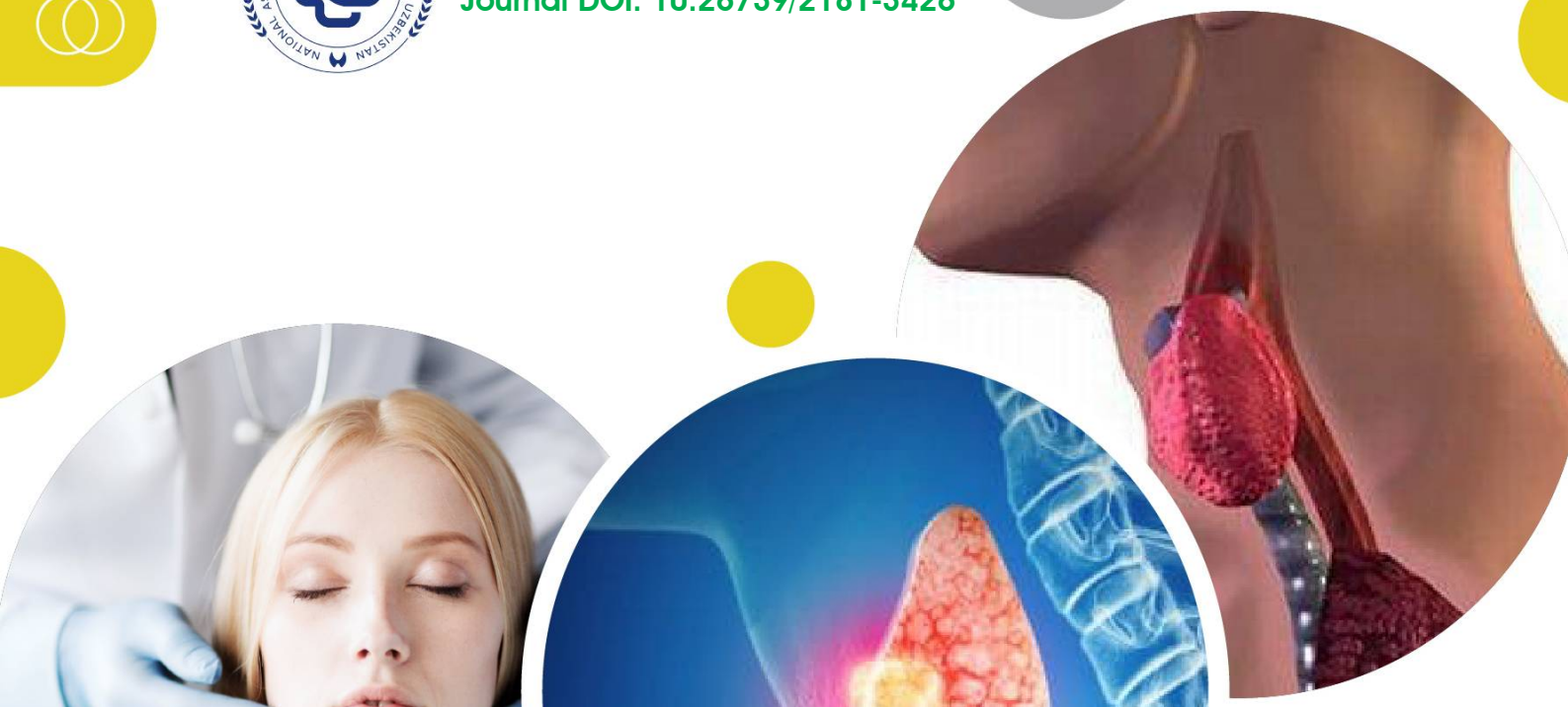

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ЦЕНТРАЛЬНО- АЗИАТСКИЙ ЭНДОКРИНОЛОГИЧЕСКИЙ ЖУРНАЛ
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PARATHYROID GLANDS: ANATOMO-PHYSIOLOGICAL ASPECTS AND HORMONES ACTION

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ANNOTATION

In review paper, the authors presented data about anatomy and physiology of parathyroid glands, molecular mechanism of parathyroid hormone action, interaction with vitamin D, its derivatives and receptors, also explained in details the role of calcitonine, FGF23, FGFRs, calcium sensing receptor CaSR and Klotho protein. Hormonal action of PTH were described in details with illustration, especially regulation of calcium and phosphorus level in the blood plasma and in bones mineralisation. Information about disturbance of mineral metabolism and involving of parathyroid glands with development of primary, secondary and tertiary pathology described. This review presented interest for family doctors, specialist physicians such as endocrinologist, nephrologist, hemodialysis doctors, surgeons, also for students and residents.

Key words: Parathyroid glands, parathyroid hormone, calcium, phosphorus, vitamin D, vitamin D receptor, FGF23, FGFRs, Klotho protein.

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ПАРАЩИТОВИДНЫЕ ЖЕЛЕЗЫ: АНАТОМО-ФИЗИОЛОГИЧЕСКИЕ АСПЕКТЫ И ДЕЙСТВИЕ ГОРМОНОВ

АННОТАЦИЯ

В обзорной статье авторы представили данные об анатомии и физиологии паращитовидных желез, молекулярном механизме действия паратиреоидного гормона, взаимодействии с витамином D, его производными и рецепторами, а также подробно объяснили роль кальцитонина, FGF23, FGFRs, кальций-чувствительного рецептора. CaSR и

белок Klotho. Подробно с иллюстрациями описано гормональное действие ПТГ, особенно в регуляции уровня кальция и фосфора в плазме крови и в минерализации костей. Описаны данные о нарушении минерального обмена и поражении паращитовидных желез с развитием первичной, вторичной и третичной патологии. Этот обзор представляет интерес для семейных врачей, врачей-специалистов, таких как эндокринолог, нефролог, гемодиализных врачей, хирургов, а также для студентов и ординаторов.

Ключевые слова: Паращитовидные железы, паратгормон, кальций, фосфор, витамин D, рецептор витамина D, FGF23, FGFRs, белок Клото.

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ҚАЛҚОН ОЛДИ БЕЗИ: АНАТОМО-ФИЗИОЛОГИК АСПЕКТЛАРИ ВА ГОРМОНЛАР ТАЪСИРИ

АННОТАЦИЯ

Адабиётлар шархида қалқон олди бези анатомия физиологияси, паратироид гормони таъмири молекуляр механизми, витамин Д, унинг рецепторлари ва хосилалари, шунингдек кальцитонин, FGF23, FGFRs, кальций-сезувчи рецептор CaSR ва Klotho оқсили билан ўзаро таъсири хақида маълумотлар келтирдилар. ПТГ нинг гормонал таъсири, айниқса қон зардобида кальций ва фосфор миқдори, хамда суяклар минерализациясидаги ўрни батафсил расмлар билан изохлаб берилди. Минерал алмашинуви бузилишларининг қалқон олди безининг бирламчи, иккиламчи ва учламчи касалликлари ривожланишидаги маълумотлар келтирилган. Ушбу адабиётлар шархи оилавий шифокорлар, эндокринолог, нефролог, гемодиализ мутахассис шифокорларига, жаррохларга, бакалавр талабаларга, клиник ординаторлар учун қизиқарлидир.

Калит сўзлар: паратироид гормон, кальций, фосфор, витамин Д, витамин Д рецепторлари, FGF23, FGFRs, Клото оқсили.

Relevance. Parathyroid glands are one of the smallest pea-sized oval shaped endocrine gland with vary of numbers from four to twelves, positioned behind thyroid glands in the neck. However, the parathyroid gland might be as usual within the thyroid gland itself, or located atypically, for ex. retrosternal, or even in the thymus rarely [23]. The parathyroid hormone (PTH) or parathyrin produces by the chief cells. PTH is synthesized polypeptide and cleaved into a ready active form within parathyroid gland. When low serum calcium detected the secretion of active PTH can be happens in a few seconds. The serum half-life of activated PTH is a very short such as two to five minutes. The main target end organs for PTH action are kidneys, skeletal system and small intestine and PTH is removed from the serum by the kidney and liver quickly [2; 12]. There are two types of PTH receptors. The first type is called parathyroid hormone 1 receptors. This receptor is activated by the 34 N-terminal amino acids of PTH which are present at high levels on bone and kidney's cells. The second type is parathyroid hormone 2 receptors which are located at high level on central nervous system, pancreas, testes and placenta's cells [23].

Purpose. By this review, the family doctors, specialist physicians such as endocrinologist, nephrologist, hemodialysis doctors, surgeons, also for students and residents would widely understand anatomo-phyioloical aspects and hormones action of parathyroid gland. To develop evidence based published articles, lectures and journal to enhance the understand, appropriate and effective clinical practice.

Materials and methods. The multidiscipline panel used to review medical literature from

January 1, 2006 to December 31,2022. Level of evidence were determined on published and upon academic thesis and lecture.

Results. PTH and mechanism of action. The main and major function of the PTH by parathyroid gland is to maintain and regulation calcium and phosphate levels. It controls within a very narrow range in tightly to make properly function of nervous and muscular system. And it was one of the first hormone to be shown to use G-protien adenylyl cyclase second messenger system [23]. In the kidney, about 250 mmol of calcium ions are filtered in the glomerular filtrate per day. Most of the physiologic calcium, about 245 mmol/d, reabsorption in the nephron takes place in the proximal convoluted tubule (most, 60-70%) and additionally at the ascending loop of Henle except in the thin segment of it. PTH targets at the distal convoluted tubule and collecting duct, directly increasing calcium reabsorption. Circulation of PTH only influences the reabsorption in the renal collecting ducts and distal tubules [2]. One of the most important effect of PTH on the kidney is inhibition of the reabsorption of phosphate from the tubular fluid, resulting in a decreasing in the plasma phosphate concentration. As form of the phosphate ion is water insoluble salts with calcium, therefore reduction and decrease of phosphate ions bring the result in more ionized calcium in the blood stream. The third important role of PTH on the kidney is stimulation to convert forms of vitamin D. (fig.1)

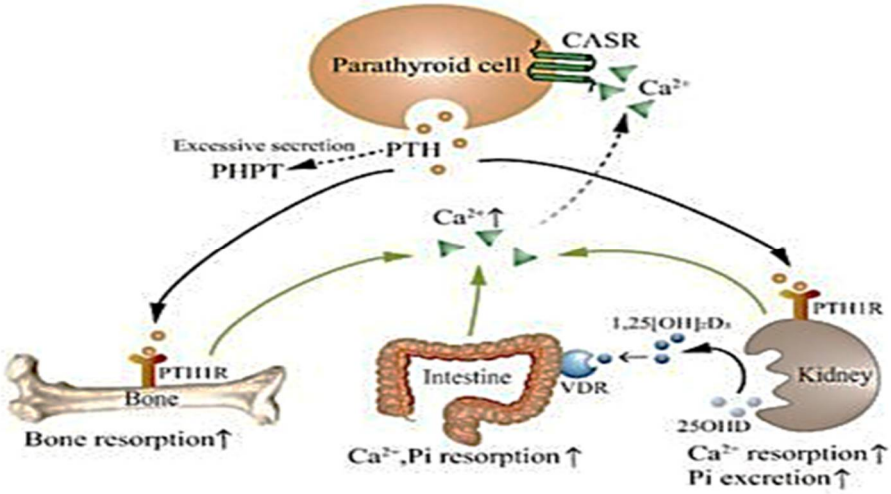

Figure 1. The physiological mechanism of Parathyroid hormone (PTH) synthesis and action.

CASR – calcium sensing receptor; PTH1R – PTH receptor type 1 in bone and kidney; PTH promotes bone absorption and the release of bone Ca 2+ , as well as the reabsorption of Ca 2+ and the excretion of Pi in the kidney. PTH can also promote the conversion of 25OHD to 1,25[OH] 2 D 3 in the kidney. 1,25[OH] 2 D 3 binds to VDR, increasing the reabsorption of Ca 2+ and Pi in the intestine. Serum Ca 2+ regulates PTH secretion by binding to CASR on parathyroid cells. PTH, parathyroid hormone; PHPT, primary hyperparathyroidism; PTH1R, PTH1 receptor; Ca 2+ , calcium ions; Pi, phosphorus; 25OHD, 25-hydroxyvitamin D; 1,25[OH] 2 D 3 , 1,25-dihydroxyvitamin D; VDR, vitamin D receptor; CASR, calcium-sensitive receptors; ↑, upregulated. Figure adopted from [21].

PTH in intestinal Ca+ absorption

By PTH, 1-alpha-hydroxylase, the enzyme, responsible for 1-alpha hydroxylation of 25-hydroxy vitamin D into active form of vitamin which is 1,25-dihydroxy vitamin D which is called calcitriol and is secreted in the circulation. This form of vitamin D is active hormone that also stimulates calcium reabsorption from the intestine via calbindin [17; 20]. By this effect of PTH, vitamin D allows absorption of calcium via both of an active energy-depended transcellular pathway and a passive paracellular pathway, which is passage of calcium through tight junctions.

PTH effects in bone

In the bone and skeleton system, PTH enhances the releases of calcium from bone. This bone resorption is indirect process where PTH binds to osteoblasts and causes increasing their expression of RANKL, receptor activator of nuclear factor-κB ligand also known as TNFSF11 [19; 24; 28]. PTH

through inhibition the osteoprotegerin, prevent its binding to RANKL as a decoy receptor, therefore prevent RANKL from interacting with RANK, known as TNFRSF11A. The resulting multinucleated cells are osteoclasts, which have ability to remodel and resorption of the bone by dissolution and degradation of hydroxyapatite and other organic material, releasing calcium into the blood.

Regulation of serum Ca+ level by PTH

On the surface of parathyroid gland's cells have calcium sensing receptors (CaSR). Mainly secretion and regulation of parathyroid hormone is through negative feedback mechanism by concentration of serum ionized calcium concentration by this CaSR which is a family C of G protein coupled receptor (GPCR). The GPCR bind extracellular calcium and it might be also found on the surface of variety of cells distributed on other organs such as in the brain, heart, skin, stomach, C cells and other tissues. When serum ionized calcium is decreased PTH is secreted. Meanwhile calcitonin is secreted when it is increased. Another mechanism of regulation of PTH secretion is by fibroblast growth factor 23. Parathyroid glands express FGF recetpors FGFR1 and FGFR3 and Klotho [2]. FGF23 decreases PTH secretion and PTH mRNA. The inhibitory action of FGF23 on PTH secretion involves both Klotho-dependent and Klotho-independent pathways. Klotho-dependent inhibition is mediated through a canonical mechanism involving MAPK/ERK, whereas Klotho-independent FGF23 regulation of PTH secretion acts through calcineurin-NFAT signaling [2; 18; 23]. By these two main mechanism PTH secretion that has a calcium branch regulated by the CaSR and a phosphate-sensing limbs that is controlled by FGF23 acting through FGFRs. These mean, the stimulators are decrease calcium in serum, mild decreasing of magnesium in serum, epinephrine and histamine, the inhibitors are increase calcium in serum and severe decrease in serum magnesium which causes hypocalcemia, symptoms of hypoparathyroidism. Increasing in serum phosphate can be stimulator and inhibitors of secretion of PTH by primarily and initially affect more on which system. By complexing with serum calcium, forming calcium phosphate, reduces stimulation of CaSR which do not able to sense calcium phosphate and it triggers increasing level of PTH, meanwhile FGF23 is produced in osteoblast from bone by increasing in serum phosphate. It binds to the fibroblast growth factor receptor of parathyroid gland and it suppresses parathyroid hormone releasing [2; 18]. (fig.2)

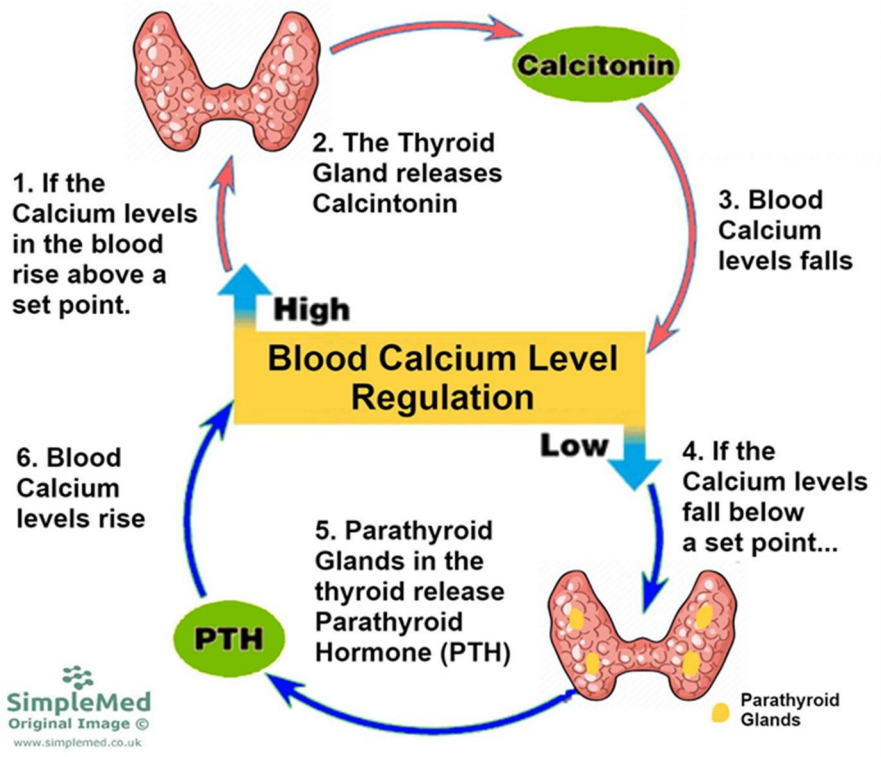

Figure 2. Blood calcium regulation by PTH.

(adopted from https://simplemed.co.uk/subjects/endocrinology/calcium-metabolism)

Primary Hyperparathyroidism (PHPT)

Primary hyperparathyroidism is the most common [8] Primary HPT is defined as hypersecretion of PTH abnormally due to parathyroid adenoma, parathyroid hyperplasia, or also rarely, parathyroid carcinoma. Approximately 85% of HPT are found to be caused by an isolated parathyroid adenoma, 15% of it is caused by diffuse parathyroid hyperplasia and less than 1% is by parathyroid carcinoma. Other causes can be including neck or mediastinal parathyroid cysts, related to multiple endocrine neoplasia. About 80% cases is benign overgrowth of parathyroid gland's tissue in single gland and 15-20% on multiple gland disorder. Parathyroid gland is involved into both two type of MEN syndromes, which have an autosomal dominant hereditary pattern with a tendency to develop tumors of the endocrine organs. Long-term treatment of lithium for patients with bipolar disorder increase risk for HTP [8]. Secondary hyperparathyroidism is referred to the compensatory hyperfunction of parathyroid glands and oversecretion of PTH due to response to hypocalcemia or peripheral resistance to parathyroid hormone. The most common cause of secondary HPT is end organ failure by chronic renal insufficiency, which leads to hypocalcemia and hyperphosphatemia.

Table 1.

Laboratory comparison by hyperparathyroidism

Hyperparathyroidism	Calcium	PTH	Vitamin D	Phosphate
Primary	↑→↓	↑→	↑	↓
Secondary	↓→	↑	↓	↑ or ↓
Tertiary	↑	↑↑	↓	↑

Key: ↑ Elevated, ↓ Decreased, → Normal

Other causes of secondary HPT can be calcium malabsorption, osteomalacia, vitamin D deficiency, or deranged vitamin D metabolism. Depending on the underlying pathology lab test values are different. In case of chronic renal failure, PTH will be elevated with decreased calcium and elevated phosphate, whereas in malabsorption and vitamin D deficiency, level of PTH is also increased but decrease both calcium and phosphate [25].

Table 2.

Causes of Hyperparathyroidism

Primary	**Secondary**	**Tertiary**
Underlying Pathophysiological Mechanism		
Enlargement of one or more glands results in hypersecretion of PTH	Excessive production of PTH in response to decreased calcium levels	Autonomous hypersecretion of PTH despite correction of the underlying cause, usually in long-lasting secondary hyperparathyroidism
Underlying cases		
➢ Parathyroid adenoma, Hyperplasia, Carcinoma ➢ MEN1 or MEN2a	➢ Renal failure ➢ Impaired calcitriol production ➢ Hyperphosphatemia	➢ Autonomous hypersecretion of parathyroid hormone ➢ Chronic secondary

➢ Familial hypocalciuric hypercalcemia ➢ Hyperparathyroid-jaw tumor syndrome ➢ Familial isolated hyperparathyroidism	➢ Decreased calcium ➢ Low oral intake ➢ Vit D deficiency ➢ Malapsorption ➢ Renal calcium loss ➢ Inhibition of bone resorption ➢ Bisphosphonates ➢ Hungry bone syndrome	hyperparathyroidism ➢ After renal transplantation

Secondary and tertiary Hyperparathyroidism (sHPT and tHPT)

Renal osteodystrophy is defined by bone disease in secondary HPT caused by kidney failure [13]. Tertiary HPT occurs rare than primary and secondary types but it is seen by continuous secretion of PTH even after previous secondary HPT despite correct and treat underlying causes. Long term secondary HPT leads to hyperplasia of parathyroid gland and loss of response of serum calcium levels. Lab test values are moderately increase PTH, normal or slightly increase calcium and decreased phosphate [25].

Main treatment of primary HPT is parathyroidectomy which is surgical remove the parathyroid tumor or adenoma under indications such as symptomatic HPT, or asymptomatic HPT with any of them 24-hour culinary calcium is over 400mg, serum calcium over 1mg/dL upper limit of normal, creatinine clearance is over 30 % below normal for patient's age, bone density is over 2.5 standard deviations below peak and patient's age is under 50 years old. The treatment of secondary HPT is directly to primary cause of hypocalcaemia firstly. In contrast, hypoparathyroidism, which is deficient or absent of parathyroid hormone secretion is an uncommon congenital or acquired condition. The most common cause of hypoparathyroidism is damage to or removal of the parathyroid glands during neck surgery, accounting for approximately 75% of cases [1; 26]. Autoimmunity targeting the parathyroid gland and, rarely, genetic disorders can also lead to hypoparathyroidism [1]. In genetic causes, such as DiGeorge syndrome is the most common cause which is associate with microdeletion in chromosome 22q11.2 and parathyroid hypoplasia [16]. Other genetic causes are autosomal dominant hypocalcemia which makes activating mutation of CaSR decreases set point and autoimmune polyendocrine syndrome type 1 which a mutiation in the autoimmune regulator gene cause destruction of parathyroid and other endocrine glands [10; 11]. By related conditions, hypoparathyroidism can be divided hypoparathyroidism, pseudohypoparathyroidism which has sub categories – type 1A, type 1B, type 2, and pseudopseudohypoparathyroidism. Main goal of treatment is maintain level of serum calcium below or within the lower limit normal range. With main aim of treatment, preserving serum phosphate level in normal, preventing increasing of serum calcium-phosphorus product, minimizing hypercalciuria, avoiding kidney stones and mineralization of soft tissues. The main treatment of hypoparathyroidism is conventional management. It consists of oral calcium such as calcium carbonate or citrate and vitamin D treatments, for example calcitriol. Thiazide diuretics for increasing calcium reabsorption at the distal tubule in kidney and supplement of magnesium also can be used.

Table 3.

Recognizing type of pseudohyperparathyroidism. Adopted from [28].

Classification	Hormone resistance	Albright osteodystrophy	GNAS gene defect	PTH infusion
PHP1a	Multiple: PTH, TSH,Gn, GnRh	Yes	Maternal mutation	↓cAMP ↓Phosphaturia
PHP 1b	PTH, TSH	No	Imprint	↓cAMP ↓Phosphaturia
PHP 1c	Multiple: PTH,	Yes	Maternal	↓cAMP

	TSH,Gn		mutation	↓Phosphaturia
PHP 2	PTH	No	Unknown	Normal cAMP ↓Phosphaturia
PPHP	No	Yes	Paternal mutation	Normal

General information of secondary hyperparathyroidism

Secondary hyperparathyroidism (sHPT) is a medical condition that excessive secretion of parathyroid hormone with an adaptive, an in many cases ultimately maladaptive process develops in associate with declining function of kidney, impaired phosphate excretion and failure to bio-activate vitamin D. Impaired of calcium and phosphorus homeostasis cause decrease phosphate excretion in kidney, increased serum phosphorus, increase levels of phosphatonin fibroblast growth factor 23, and reduced synthesis of calcitriol which is the active form of vitamin D. Combined these changes lead to increase synthesis and secretion of PTH and parathyroid hyperplasia, contributing to the development of vicious cycle [25]. By this process, the chronic kidney disease, end-stage of renal disease is the most frequently associate with sHPT and the most common reason is vitamin D deficiency. The other causes can be malabsorption such as small bowel disease, chronic pancreatitis, malabsorption-dependent bariatric surgery which all leads impairment of reabsorbed fat-soluble vitamin D. Also, few other causes can be from inadequate dietary intake of calcium, vitamin D deficiency, or steatorrhea [17]. The major symptoms of sHPT are pruritus and osteodynia, depression and concentration difficulties. Further without proper treatment, patients have an increased risk of all causes and cardiovascular mortality by renal osteodystrophy, vascular calcification and cardiovascular damage. General optional treatments of sHPT are calcimimetics, vitamin D supplements, phosphate binders and surgical method which is parathyroidectomy. The achieving current targets for the key mineral parameters in the management of sHPT and optimal treatment is very individual by patient and still challenging for endocrinologists, endocrine surgeons and nephrologist.

Secondary hyperparathyroidism with chronic kidney disease

Secondary hyperparathyroidism which is caused by chronic renal disease is also referred to renal hyperparathyroidism (rHPT) due to manifests as one of two types of renal osteodystrophy. rHPT is common complication of chronic kidney diseases which is characterized by elevated parathyroid hormone levels resulting in metabolic abnormality in homeostasis of calcium, phosphate and vitamin D. rHPT is to seen into two types of hyperparathyroidism classically. Most of cases are in secondary hyperparathyroidism. sHPT is compensatory mechanism of parathyroid glands, ultimate treatment of underline such as renal transplantation leading cause possibly resolves that normalization of calcium and phosphorous homeostasis. In tertiary hyperparathryroidism is seen when longstanding sHPT and develops autonomous PTH secretion with association of increase serum calcium level. Tertiary hyperparathyroidism is founded up to 30% of ESRD patients who underwent renal transplant [15]. It is classically from parathyroid hyperplasia, however there are also studies which have shown up to 20% of patients have single or more adenomas [15]. The severity of rHPT is very variable and is also easy to seen in countries with high rates of ESRD because of diabetes mellitus type 2 and uncontrolled hypertension. The worldwide prevalence of end-stage renal disease is 0.1% and 14.5% of the population have chronic kidney disease including generally 660,000 patients with end-stage renal disease who receive dialysis treatment [13]. Chronic kidney disease has high prevalent issue as most often consequence of chronic disease, diabetes, hypertension. About 40% of patients with diabetes develop to have diabetic nephropathy. Five stages of CKD are used to stratify patients based on the degree of kidney function and role as markers to predict the development of comorbidities of CKD, such as sHPT. Secdondary hyperparhtyodism is generally develop in stage 3 CKD which is estimated glomerular filtratiation rate is under 60mL/min/1.74m^2 and most of hemodialysis patients have sHPT [15,17].

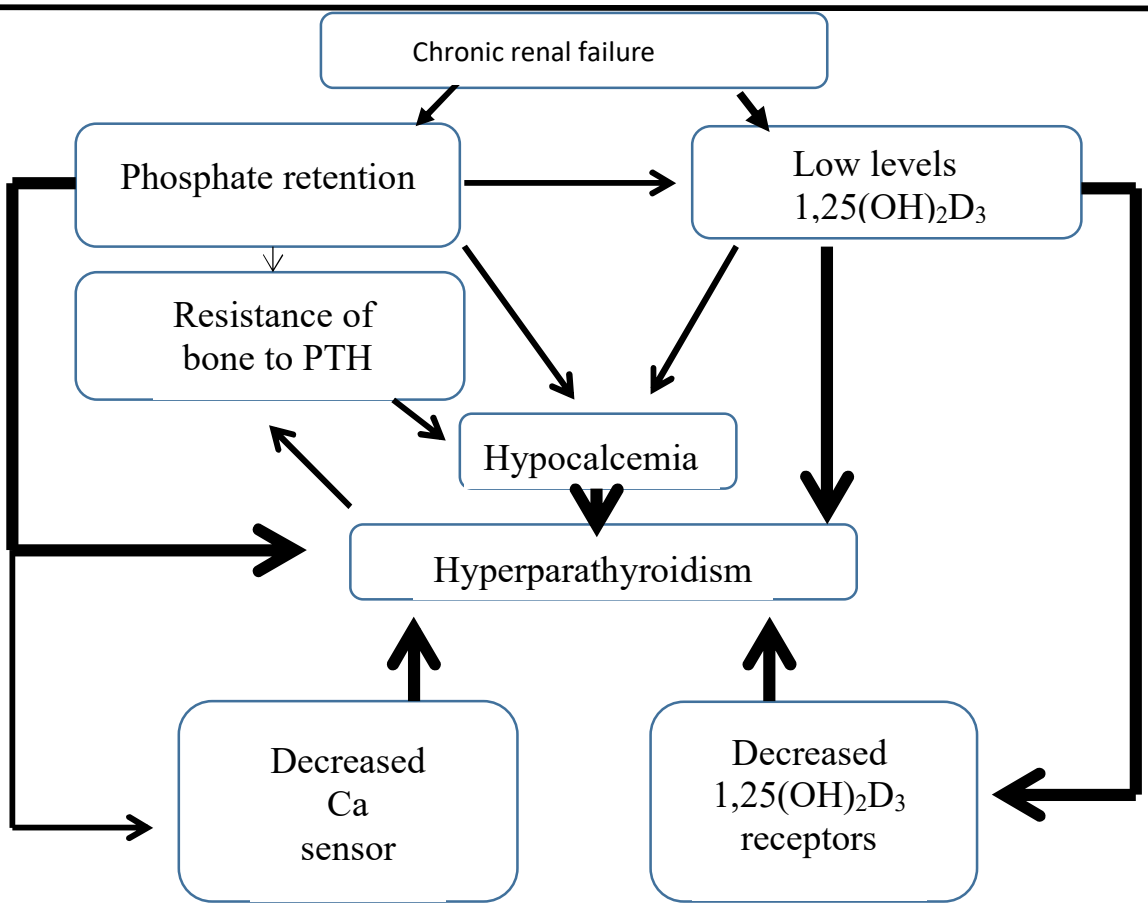

Figure 3. Scheme how chronic renal failure leads to hyperparathyroidism.

CKD patients under classified stage 3, stage 4, or stage 5 are at risk for rHPT and increase the risk with severe stage of CKD, and affects 40% of patients with stage 3 CKD and 82% of patients with stage 4 CKD [15]. rHPT has important roles in the pathogenesis of CKD-mineral bone disorder. CKD-MBD is a systemic disorder of mineral and bone metabolism by CKD manifested by either one or combination of several factors such as biochemical abnormalities of calcium, phosphorus, PTH, or vitamin D metabolism, klotho, phosphate, fibroblast growth factor 23 and sclerostin,; abnormalities in bone turnover, mineralization, volume, linear growth, or strength; cardiovascular or other soft tissue calcification [15]. sHPT causes several outcomes including renal osteodystrophy and progressive vascular calcification which is leaded to the patients have high risk of developing cardiovascular diseases and bone complication like skeletal fractures and death [15]. Therefore, early diagnosis and proper treatment is necessary to reduce risk and progress to late severe complications and mortality. The biochemical abnormalities of CKD with mineral and bone disorder and renal osteodystrophy may begin in CKD stage 3, but the rate and severity of changes are very variable and individual among patients. Because of these studies, monitoring serum levels of PTH, calcium, phosphorus and alkaline phosphatase is strongly recommended to start at CKD stage 3 and in children at CKD stage 2 [15]. Last decades, medical management is improved in vitamin D analogs, phosphate binders, and calcimimetic drug to expand option of treatment for rHPT patients, but still surgical treatment is required to treat by depending on conditions of patients.

Secondary hyperparathyroidism in dialysis

Secondary hyperparathyroidism is one of the most prevalent in patients with end-stage renal disease. The more severe stage of ESRD, the more frequency rate to have sHPT. Therefore, the last stage of ESRD, in the group of patients under dialysis treatment, sHPT is more often seen than other stage of ESRD. Most cases of patients with dialysis require to receive any type of dialysis last lifelong without kidney transplantation, and in reality still there are many reasons and problems to receive kidney transplantation, that's why dialysis is the most common alterative treatment for patients with

ESRD stage 4 to 5. The prevalence of renal hyperparathyroidism in dialysis population is from 12% to 54% [14]. and another study shows that up to 75% of patients under hemodialysis treatment have increases PTH, consistent with sHPT, and 40% to 50% of patients who is initiating hemodialysis already have indicative of mild to severe sHPT which is 150 to 600 pg/mL in PTH. the rate of rHPT in dialysis is highly effected on countries, race, proper and early prevention with treatment [14]. There is no clear survival benefit of undergoing parathyroidectomy for hemodialysis or peritoneal dialysis for patients who need kidney transplantation. However, still dialysis has significantly effect on regulation of PTH levels, hemoglobin, ferritin, albumin, cholesterol and other bio-chemical elements which are attempted to cause of sHPT [14]. Until now with dialysis treatment and other severe disease, Suppression of PTH to strictly under normal level by reference study is difficult in patients [14; 15]. By this reason the clinically and some guideline address intact PTH optimal level would be associated with normal bone histology are between 1.5 and 2.5 times the upper reference limit which is roughly 100 to 150 pg/mL [15; 22].

Pathophysiology. The pathophysiology of secondary hyperparathyroidism is complex and associated with several factors besides only involving parathyroid glands. The core part of pathogenesis is abnormal regulation and homeostasis of calcium. Other factors which are involving pathophysiology are phosphate retention, low serum calcium, hyperphosphatemia, 1,25-Dihydroxyvitamin D deficiency, reduction of vitamin D receptors and calcium-sensing receptors in parathyroid, intestinal calcium malabsorption and mRNA-binding protein activities modulating parathyroid hormone transcripts [15; 22]. Hyperplasia of parathyroid is present frequently in sHPT in CKD progression towards to stage 5 by decreases in CaSr and VDR expression [7]. In early kidney failure, modification in metabolism of vitamin, decrease level of calcitriol and moderate decreases in ionized calcium causes increases synthesis and secretion of PTH. By progressing CKD, the number of vitamin D receptors and calcium sensitive receptor are decreased. This results lead to more resistant to calcitriol and calcium in parathyroid glands. and even at early stage in the development of HPT, by variable under expression of CaSr, located on the surface of the chief cells of the parathyroid gland, and VDR the rendering the parathyroid cells are not able to respond to ambient calcium and/or calcitriol properly. In CKD, decreased serum calcium level is result in continuing inactivation of the CaSr, reduced signaling thought the CaSr and increased PTH synthesis and secretion [18]. By PTH secretion is increased, calcium is released from bone tissue, enhancing phosphate excretion in the presence of a functioning kidney [22]. This processes in parathyroid gland depend on rapidity and duration of the hypocalcaemic stress. PTH release by response to calcium events within seconds to minutes following by signal thorough the CaSr, chronic hypocalcaemia and hyperphosphagaemia stimulate PTH gene expression and subsequent PTH synthesis within hours to days and proliferation of parathyroid cells occurs over days to weeks [7; 18; 22]. Independent of calcium and calcitriol, phosphorus induces hyperplasia of the parathyroid gland and increase PTH synthesis and secretion by post-transcriptional mechanism. The nuclear VDR suppress PTH gene transcription, PTH is also regulated after transcription by binding of stabilizing RNA binding proteins to the 3' untranslated region of the PTH transcript [18]. The main facts of phosphorous homeostasis part in transcriptional mechanism are fibroblast growth factor-23 and its receptor fibroblast growth factor receptor 1. The retained phosphate stimulates osteocytes and osteoblast to synthesize FGF23. FGF23 binds to fibroblast growth factor receptor 1, in the presence of the required to co-receptor Klotho transmembrane protein, a Klotho, as a Klotho-FGF receptor complex. FGF23 decreases the type II sodium–dependent phosphate cotransporters Sodium-dependent phosphate transport protein, also known as Na^+-Pi cotransporter 2a and 2c in the proximal tubule of the kidney, in this manner, increasing both serum FGF23 and PTH in patients with CKD inhibit and decrease phosphate reabsorption in proximal tube and maintain normal level of phosphate in blood in most patients until the glomerular filtration rate falls under 20 ml/min and further stimulating phosphaturia [18]. With progressive CKD, production of Klotho is also decreased. It leads the limitation of effectiveness of FGF23/Klotho to correction phosphate retention. Further stimulation and increasing production of FGF23 are resulted by development of over hyperphatemia and increasing of 1,25-dihydroxyvitamin D and parathyroid hormones (fig.4).

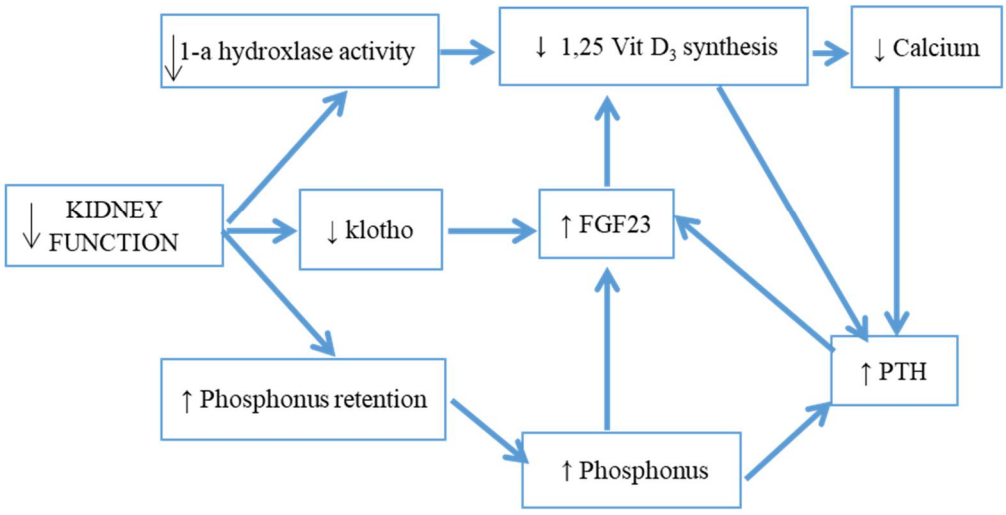

Figure 4. Pathophysiology of secondary hyperparathyroidism in dialysis.adopted from [4]

FGF23 also reduces $1,25(OH)_2D$ production in the kidney by inhibition of the 1-a-hydroxylase and stimulates $1,25(OH)_2D$ degradation by stimulating 24-hydroxylase [4; 5]. Absorption of calcium and phosphorus in gut is decreased due to $1,25(OH)_2D$ promotion intestinal absorption of them. The decreased serum calcium calcitriol concentrations are sensed by the VDR and CaSr of the parathyroid cells which cause cell proliferation and increase PTH production (fig.1). Increase phosphate level in blood also inhibits CaSr directly and stimulates PTH secretion [59]. FGF23 binds to the Kloth-FGF23 receptor in the parathyroid to inhibit PTH however, decreasing Klotho by progression of CKD and reducing kidney function leads to ability of FGF23 to decrease PTH concentration is disappeared [4]. PTH promotes bone resorption with release of calcium and phosphate and increase 1-a-hydroxylase manifestation in the proximal tubules of kidney to help maintain concentration of normal serum calcium. Continuous phosphate retention and hypocalcemia lead to sustained and progressive increase in PTH production. With these all process, they lead to hyperplasia of parathyroid gland further expending sHPT.

Progression of secondary hyperparathyroidism and complications

In the early stage of chronic kidney disease, usually the patients may have only slightly higher PTH level than reference values without any changes in their serum calcium and phosphate levels. Serum levels of phosphate and calcium are regulated with helping by increased levels of FGF23 in these patients [27].

Prolonged parathyroid stimulation by pathophysiology and progression of CKD cause diffuse polyclonal hyperplasia initially followed by monoclonal nodular hyperplasia [6,9]. signal transduction throughout CaSr is main dominant role of determinant of parathyroid cell proliferation and parathyroid gland hyperplasia [9]. Proliferation of parathyroid cell is associated with a decrease in CaSr and VDR expression. Vitamin D is a potent inhibitor of PHT synthesis, a reduction in VDR expression also inhibits the vitamin D-mediated signals which suppress PTH synthesis and release. Expression VDR is effected by low calcium and calcitriol levels directly. Parathyroid cells in advanced secondary hyperparathyroidism are transformed into a severe nodular hyperplastic state, a decline in VDR expression reduces the efficiency of vitamin D receptor activators in up-regulating the transcription of the CaSr gene and in inhibiting parathyroid cell proliferation on parathyroid gland and PTH secretion [3]. The outcome of severe hyperparathyroidism possibly cause hypercalcemia and hyperphosphatemia due to calcium and phosphorus efflux from bone. Increase level of calcium and phosphorous with sHPT is associated with development of vascular calcification which is high risk factor of increasing morbidity and mortality. Transcription factors including Cbfa-1/RUNX2 and MSX-2 have been identified in vascular smooth muscle cells adjacent to areas of calcification in CKD patients [3]. Bone proteins such as osteoponitn, bone sialoprotein, type 1 collagen, osteonectin, and

alkaline phosphatase are localized to sites of extra skeletal calcification. FGF23 is also one of key proteins to explain the complex pathogenesis of vascular calcification. Inorganic phosphate transport into the cells via type III Na-Pi co transporter increased as the extracellular phosphate concentration increased. The increase in the intracellular phosphate concentration induced the expression of marker genes of apoptosis and osteogenic/chondrogenic cells in the vascular wall cells, which resulted in calcification [3; 20]. Age and dialysis duration of patients are associated with increasing risk of vascular calcification. Mostly, duration of dialysis is not in proportion with age. This condition characterized by calcification of the vascular media called Mönckeberg sclerosis rather than calcification of the vascular intima. The onset of blood vessel calcification in dialysis patients is mainly, caused by sHPT and leads to abnormal calcium and phosphate metabolism. Calcification of the iliac artery and abdominal aorta are critical predictors of mortality from cardio vascular system in dialysis patients [3; 20].

Renal Osteodystrophy is mineral and bone disorder by complication of CKD and sHPT. It impairs bone fragility and fracture. Old age, duration of dialysis, female gender, white race and lower body weight are main risk factors which increases fracture. In CKD patients, ROD manifests as alterations in bone morphology, such as osteitis fibrosa cystica, hyperparathyroidism-related bone disease, osteomalacia, adynamic bone disease, and mixed uremic osteodystrophy. ROD represents histopathologic changes observed in bone and is typically characterized by changes in bone turnover, volume, and mineralization [20].

Thus, the regulation of calcium and phosphorus metabolism in the body is strictly controlled by the level of PTH, on the one hand, and the level of vitamin D, on the other hand, with the participation of genetic factors, growth factors, and regulatory proteins. Violation of mineral metabolism in the body is accompanied by violations of bone metabolism with the development of osteoporosis and fractures. Understanding the factors regulating mineral metabolism will help in early diagnosis, prevention of the development of primary, secondary and tertiary hyperparathyroidism in patients with genetic and endocrine diseases, malabsorption, who are on hemodialysis.

Conclusion

Parathyroid gland has complex mechanism and linking with many other organs and regulation systems. Primarily by function of parathyroid gland, the sensitive process of calcium and phosphate homeostasis. According to the anatomy of parathyroid gland, preoperative biopsy of parathyroid shouldn't be performed and also considered possibility of multi-gland problem and diseases. Understanding origin and pathophysiology are the key to treatment of hyperparathyroidism due to similar lab results but the treatment of choice is depending on type of HPT.

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