ISSN: 2181-3426
Journal DOI: 10.26739/2181-3426

MARKAZIY OSIYO ENDOKRINOLOGIK JURNALI

ЦЕНТРАЛЬНО АЗИАТСКИЙ ЭНДОКРИНОЛОГИЧЕСКИЙ ЖУРНАЛ

CENTRAL ASIAN ENDOCRINOLOGICAL JOURNAL

VOLUME 3
ISSUE 2
2023

ISSN: 2181-3426

Journal DOI: 10.26739/2181-3426

MARKAZIY OSIYO ENDOKRINOLOGIK JURNALI

3 ЖИЛД, 2 СОН

ЦЕНТРАЛЬНО АЗИАТСКИЙ ЭНДОКРИНОЛОГИЧЕСКИЙ ЖУРНАЛ

ТОМ 3, НОМЕР 2

CENTRAL ASIAN ENDOCRINOLOGICAL JOURNAL

VOLUME 3, ISSUE 2

Учредитель:

Национальная Ассоциация эндокринологов Узбекистана.

Tadqiqot.uz

ТОШКЕНТ-2023

MARKAZIY OSIYO ENDOKRINOLOGIK JURNALI

ЦЕНТРАЛЬНО АЗИАТСКИЙ ЭНДОКРИНОЛОГИЧЕСКИЙ ЖУРНАЛ | CENTRAL ASIAN ENDOCRINOLOGICAL JOURNAL

№2 (2023) DOI http://dx.doi.org/10.26739/2181-3426-2023-2

Page Maker | Верстка | Сахифаловчи: Хуршид Мирзахмедов

Контакт редакций журналов. www.tadqiqot.uz
ООО Tadqiqot город Ташкент,
улица Амира Темура пр.1, дом-2.
Web: http://www.tadqiqot.uz/; Email: info@tadqiqot.uz
Тел: (+998-94) 404-0000

Editorial staff of the journals of www.tadqiqot.uz
Tadqiqot LLC the city of Tashkent,
Amir Temur Street pr.1, House 2.
Web: http://www.tadqiqot.uz/; Email: info@tadqiqot.uz
Phone: (+998-94) 404-0000

МУНДАРИЖА | СОДЕРЖАНИЕ | CONTENT

ISSN: 2181-3426
www.tadqiqot.uz
O'RTA OSIYO ENDOKRINOLOGIK JURNALI
ЦЕНТРАЛЬНО АЗИАТСКИЙ ЭНДОКРИНОЛОГИЧЕСКИЙ ЖУРНАЛ | CENTRAL ASIAN ENDOCRINOLOGICAL JOURNAL

Ju Seunghwan,
Ismailov S.I.,
Shamansurova Z.M.
Tashkent pediatric medical institute, Uzbekistan.

SECONDARY HYPERPARATHYROIDISM: PATHOGENESIS AND CLINICAL ASPECTS

http://dx.doi.org/10.5281/zenodo.8264458

ANNOTATION

In review paper, the authors presented data about hyperparathyroidism, primary, secondary, tertiary, their causes, clinical future and diagnosis. Parathyroid hormone and mechanism of action was described in details with illustration. Authors described causes leading to primary, secondary and tertiary hyperparathyroidism, presented differentiation of symptoms and signs in the tables and schemes. Review consist data from literature about principles of medical and surgical treatment, drugs classes and compared their mechanisms of action, indications for surgery and preparation before surgery and observation. This review presented interest for family doctors, specialist physicians such as endocrinologist, nephrologist, hemodialysis doctors, surgeons, also for students and residents.

Key words: Hyperparathyroidism, primary, secondary, tertiary, parathyroid hormone, calcium, phosphorus, vitamin D

Ju Seunghwan,
Исмаилов С.И.,
Шамансурова З.М.
Ташкентский педиатрический медицинский институт, Узбекистан.

ВТОРИЧНЫЙ ГИПЕРПАРАТИРЕОЗ: ПАТОГЕНЕЗ И КЛИНИЧЕСКИЕ АСПЕКТЫ

АННОТАЦИЯ

В обзоре представлены данные о гиперпаратиреозе первичном, вторичном, третичном, их причинах, клиническом течении и диагностике. Паратиреоидный гормон и механизм его действия были подробно описаны с иллюстрациями. Авторы описали причины, приводящие к первичному, вторичному и третичному гиперпаратиреозу, представили дифференциацию симптомов и признаков в таблицах и схемах. Обзор включает литературные данные о принципах медикаментозного и хирургического лечения гиперпаратиреоза, классах препаратов и сравнении их механизма действия, показаниях к операции и предоперационном лечении и наблюдении. Этот обзор представляет интерес для семейных врачей, врачей-специалистов, таких как эндокринологи, нефрологи, врачи гемодиализа, хирургов, а также для студентов, магистров и ординаторов.

Ключевые слова: Гиперпаратиреоз, первичный, вторичный, третичный, паратиреоидный гормон, кальций, фосфор, витамин Д

Ju Seunghwan,
Исмаилов С.И.,
Шамансурова З.М.
Тошкент педиатрия тиббиёт институти, Ўзбекистон.

ИККИЛАМЧИ ГИПЕРПАРАТИРЕОЗ: ПАТОГЕНЕЗ ВА КЛИНИК АСПЕКТЛАРИ

АННОТАЦИЯ

Адабиётлар шархида бирламчи, иккиламчи, учламчи гиперпаратиреоз хақида, уларнинг сабаблари, клиник кечими ва ташхислаш хақида маълумотлар келтирилган. Паратиреоид гормон ва унинг таъсир механизми расмлар билан кўрсатилган. Муаллифлар бирламчи, иккиламчи ва учламчи гиперпаратиреозга олиб келувчи сабаблар, симптом ва белгиларни дифференциал ташхисини жадвал ва схемаларда келтирганлар. Мақолада гиперпаратиреозни дори воситалари ва жаррохлик усули билан даволаш даволаш тамоиллари, дори воситалари турлари, таъсир механизмларини солиштириш, жаррохликка кўрсатма ва жаррохликкача ьўлган тайёргарлик, назорат хақида адабиётлардаги маълумотлар келтирилган. Бу мақола оила шифокорлари, эндокринологлар, нефрологлар, гемодиализ шифокорлари, жаррохлар каби мутахассис шифокорлар, хамда талабалар ва ординаторлар учун мўлжалланган.

Калит сўзлар: Гиперпаратиреоз, бирламчи, иккиламчи, учламчи, паратироид гормон, кальций, фосфор, витамин Д

Introduction. Secondary hyperparathyroidism usually result of excess parathyroid hormone (PTH) secretion due to parathyroid glands hypertrophy or adenoma and frequent among patients kidneys insufficiency, especially those on programmed hemodialysis. Excess secretion of PTH in that patients happened as a response to low serum calcium. 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 [14,16]. Secondary hyperparathyroidism (sHPT) is a medical conditions with excessive secretion of PTH which is adaptive 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 decreased phosphate excretion in kidney, increased serum phosphorus, levels of phosphatonin fibroblast growth factor 23 (FGF), 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 [37]. 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 [33]. 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.

Clinical features and evaluation. In patients with sHPT distrubances in phosphorus and calcium metabolism will affect the body with specific clinical signs and symptoms. Due to first reflection seen in musculoskeletal system with pains and crumps, bone remodeling and mineralization are affected [30]. This leads to bone deformation, bone pain, and bone fractures in extreme cases. Deformation and abnormal mineralisation can be seen in chest wall, pelvic bones, hip joints, and bones of lower extremities and increased stress and fractures [10,19].

Calcification is caused by high levels of PTH, calcium, and phosphorus induced by high levels of calcium in dialysate and phosphate binders [10]. Due to abnormal calcium metabolism calcifications can affected of arterial walls, in the heart, myocardium, aortic, and mitral valves and can lead to increased cardiovascular events such as ischemia, left ventricular dysfunction, congestive heart failure, arrhythmias, and death [27,40]. Also viscera, periarticular tissue, cutaneous tissue, the eye, red-eye syndrome, muscle weakness, and intense pruritus can be noted [30]. Pruritis is especially seen in renal diseases as a result deposition of calcium and phosphorus on the skin. In result, abnormal microcirculation, thrombosis, ischemia, with increased risk of infections, sepsis, and mortality [10].
Evaluation of sHPT include measure of blood PTH, calcium, phosphorus, vitamin D levels, and kidney function.
Kidney Disease for Improving Global Outcomes (KDIGO) 2017 recommends systematically performing bone mineral density in dialysis patients with bone mineralization disorders to assess the risk of pathological fracture, signs of osteodystrophy, Osteomalacia, Osteosclerosis [4, 22, 24].

Treatment and management. The main treatments of secondary hyperparathyroidism are divided into two methods. First method is pharmacological treatment initially, and the second method is surgical treatment. The Kidney Disease-Improving Global outcomes (KDIGO) Chronic Kidney Disease-Mineral Bone Disease guideline is leading recommendation of treatment for secondary hyperparathyroidism currently. However there is no still firm guidelines or consensus have been established in nephrologist and endocrine surgeon's field. Ultimate aim of treatment is that reduce morbidity and mortality associated with sHPT. Current medical treatment is following three steps; reduction of phosphorus untaken by dietary restriction or use phosphate binders, control and enhance activation of the circulating levels of calcium by using agent for modify the CaSr and control PTH level with using vitamin D metabolites such as calcitriol and newer vitamin D analogues. Bisphosphonate is used in limiting the large rate of bone resorption in severe sHPT if there is only bridge to more definitive resolution of the sHPT. This use of bisphosphonates might fall outside the licensed indications because their very slow removal from bone which carries the risk of inducing low-turnover bone disease especially the patients who are required under ultimately surgical treatment. Parathyroidectomy is the surgical treatment which is used last resort of strategy treatment after failure of medical treatment or severe condition of sHPT. All approach of treatment is potentially improve biochemical abnormality and other surrogate markers, for example bone histology The target and goal of treatment is maintaining level of serum calcium, serum phosphrous and PTH within clinical acceptable range. The reason why acceptable range is many patients are not able to fully control fixed normal range in CKD, dialysis [11].

Pharmacological treatment. Persistent hyperphosphatemia cause reduces the effectiveness of vitamin D therapy and related with phosphorus level and mortality with sHPT. Low phosphorus diet and phosphate binders is used for maintaining serum calcium and phosphorous in normal rage for sHPT. The vegetarian products usually suggested to limit phosphate intake as well as protein restriction [21]. As progression of sHPT diet not usually insufficient to completely control of serum phosphate levels, wide range of phosphate binders are used. Limit aluminum based phosphate binders are chosen in case of severe hyperphosphatemia and for a short period of time. Calcium free phosphate binders such as sevelamer and lanthanum carbonate, lowering the level of serum phosphate and are associated with lower serum calcium and PTH control (Table 4). But also another study shows that there is no significantly related effects on serum calcium and reduce circulation of PTH levels [1,36]. There is study and data show that phosphate restriction and calcium-free phosphate binders might reduce FGF23 [8]. And it also may accelerate vascular calcification deposition. That's why still phosphate binders are limited to use of treatment for established sHPT, even though hyperphosphatemia has an important role in the pathogenesis of early sHPT. Even there is lack of evidence the apparently beneficial effects of it, the surrogate markers to improve to treatment effects and patient outcomes.
Vitamin D compounds such as VDR activators such as calcitriol or nutritional like prodrug, alfacalcidol, doxercalciferol (the vitamin D2 equivalent of alfacalcidol), 22-oxacalcitriol, or

paricalcitol are used for managed defieiency of endogenous vitamin D and in CKD stage 3 to 5 patients (table 4).

Table 4.

Options of Phosphate binders

Pharmacological agents	Drugs name	**Initial dose**	**Side effects**
Calcium-containing	Calcium acetate	667-1334 mg	Nausea,vomiting, hypercalcemia
	Calcium carbonate	500-1000 mg	Nausea, vomiting, diarrhea, dyspepsia, abdominal pain,
Non-calcuim-containing	Sevelarmer hydrochloride/carbonate	800-1600 mg TID with meals	Headache, diarrhea, stomach upset
	Lanthanum carbonate	1,500mg daily	Diarrhea, nausea, abdominal pain, vomiting

These active viamin D compouds activate all VDR, albeit inderctly in case of alfacalcidol and doxercalciferol. By international guideline the correction of nutritional vitamin D deficieny as first line therapy to counteract the onset and progression of CKD-MBD in predialysis patients. Independently from the type and dose of nutritional vitamin D adopted, 25(OH)D levels should not exceed 100 ng/mL, and particular caution should be paid while supplementing patients at high risk of 1-α-hydroxylase activity, as kidney transplant patients and those affected by sarcoidosis or B-cell lymphoma [3]. In nondialysis CKD patients, it effects VDRA on counteracting sHPT. Selective VDRAs such as paricalcitol and doxercalciferol provide with a lower risk of positive calcium and phosphorus balance. In hymodialysis patients, doxercalciferol is to effect in reducing PTH, but there is also side effect, which is incidence of hypercalcemia during treatment. Paricalcitol VDRAs largely used to treat in sHPT in dialysis patients. The mechanism resistance is decreased VDR expression in parathyroid cells or failure of the calcitrol-VDR complex to interact with the vitamin D response element of its target genes [2]. Vitamin D compounds also can control sHPT better in patients with moderately increased glands and less well with enlarged glands. That is why size of parathyroid gland is one of main indication for success or failure of treatment. When there is low active vitamin D exposure leads increased pro-inflammatory cytokines, matrix metalloproteinases and decrease in protective factors of endothelial cells, and high dosage of Selective VDRAs is purported to limit calcitriol in CKD patietns at higher cardiovascular risk such as arterial stiffness, left ventricular hypertrophy, medial calcification and also hypercalcemia. Because of widespread genomic; VDR or the 25-hydroxyvitamin D 1α hydroxylase enzyme effect elicited by VDR activation, it also can be used not only treatment for sHPT but also proteinuria, left ventricular hypertrophy and anemia.

Table 5.

Options of vitamin D compounds

Pharmacological agents name	**Dose formulation**	**Initial dose**	**Side effects**
Calcitriol	Oral(0.25μg capsules)	0.25 μg daily	Hypercalcemia, headache, nausea, rash
	Injectable(1μg/mL)	1-2 μg 3 times weekly or every other day	Weakness, headach, dry mouth, muscle, bone pain

Doxercalciferol	Oral(0.5,1.0,2.5 μg capsules)	1 μg daily (predialysis) 10μg 3times weekly at dialysis	Edema, headache, malaise, dyspepsia, nausea
	Injectable 4 μg/2mL	4μg 3 times weekly at the end of dialysis or every other day	Dizziness, dyspnea,
Paricalcitol	Oral(1,2,4μg capsules),injectable	1-2μg daily (PTH ≤500 pg/mL) or 2-4μg every other day (PTH > 500 pg/mL)	Diarrhea, hypertension, dizziness, vomiting

Calcimimetics are a newer class of agents for the treatment of sHPT in patients who is under dialysis and kidney transplataion (table 6). This class bind and positive activate, modulators of the CaSr, increase the absorption of both calcium and phosphorous from the gut and reduce the synthesis of PTH [76&&,29].It is interacting with the membrane-spanning domain of the receptor to induce compomational changes that improve signal transduction. This change causes increasing sensitivity to extracellular calcium and subsequently to decrease PTH level's circulation. There is relation to their activity allosteric activator than agnoists at the CaSr [29].

Table 6.

Options of calcimimetic

Pharmacological agent name	**Dose formulation**	**Initial dosage**	**Side effects**
Cinacalcet	30,60,90 mg tablets	30mg once daily	Nausea,vomiting,diarrhea

Calcimimetics can inhibit to develop and progress of parathyroid hyperplasia by reduction the numer of cells in the S phase, proliferatinf cell nuclear antigen-positive cells and overall parathyroid cell numbers [7]. The mechanism and time of calcimimetic effect on PTH is difference with vitamin D. In case of vitamin D, it reduces PTH gene transcription and hormone synthesis over severe hours to days, while cinacalcet inhibits PTH secretion within minutes to 2 hours in sHPT. Metabolism by cytochrome P-450 system enzymes results in a cyclical pattern of serum PTH levels during continued administration of cinacalcet via anabolic effects on bone. Activation of the CaSr by calcimimetics decreases PTH mRNA stability throughout the post-translational modification of the PTH-mRNA binding protein AUF1 [12,23]. The common side effect of it is hypocalcemia due to decrease mobilization of calcium from caused by reduced PTH.

Surgical treatment. Parathyroidectomy is the surgical remove one or more number of parathyroid glad to patients who has high level of parathyroid hormone. It is only definitive main treatment method for primary hyperparathyroidism. The basic parathyroidectomy approach by surgery is that opens all four glands and removes the adenoma(s) according to gland size by clinical observations.

Indication. The main indication for parathyroidectomy in primary hyperparahyriodism a condition in which one or more of the parathyroid glands produce excessive parathyroid hormone with the condition of significant symptoms or it affects the kidneys such as nephrocalcinosis or osteoporosis, and under 50 even there is no any symptoms. In secondary hyperparathyroidism, it's recommended to patients with severe CKD leads to overact parathyroid gland due to compensate low calcium and vitamin D. Despited of all medical treatment, calcium and phosphate levels still elevate and it causes worsening bone disease or calcium deposition in the wall of blood vessels such as calciphylaxia. The patients under dialysis treatment can improve their survival rate by parathyroidectomy [26]. The Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines recommend when patients with severe hyperparathyroidism (persistent serum levels of intact PTH >

800 pg/mL (88.0 pmol/L]), combined with hypercalcemia and/or hyperphosphatemia refractory to medical therapy should receive surgical treatment [38]. However, guidelines by the Japanese Society for Dialysis Therapy (JSDT) recommend that in case of severe hyperparathyroidism (persistent serum levels of intact PTH >500 pg/mL), accompanied with hypercalcemia (serum calcium >10.0 mg/dL) and/or hyperphosphatemia (serum phosphate >6.0 mg/dL) refractory to medical therapy has to be considered surgical treatment [39].

Surgical approach and technique. The optional approach and tactics of parathyroidectomy are three mainly; subtotal parathyroidectomy, total parathyroidectomy with auto-transplantation typically into the forearm and total parathyrpidectomy without auto-transplantation. K/DOQI guideline and most researchers and experts recommend subtotal parathyroidecomy and total parathyroidecomy with auto-transplantation There is no solid scientific evidence about what kind of surgical approaches among sPTX, tPTX+AT and tPTX is the best or more effective outcome regardless of many other studies and debated [84]. Choosing specific surgical method is based on expected procedure outcome and patient's clinical condition and severity. Generally sPTX is preferred procedure in case of patients have higher chance to develop hypoparathyroidism than recurrent hyperparatroidism after operation, while tPTX+AT or tPTX is chosen when patients have expectation to have high risk of recurrent hyperparathyroidism. By this means, in younger potential kidney transplantation treatment recipients, sPTX with leftover gland is treatment of choice as hypoparathyroidism possibly develop after successful kidney transplantation. On the other hands, for old without transplantation candidates who have permanent exposure to uremia and history of exposure to aluminum tPTX+AP is preferred to avoid hypoparathyroidism after operation and resultant worsening of aluminum bone disease. Even though resection of autograft in the arm is easier than reexploration of remnant parathyroid gland in neck, there are case uncontrolled local tissue and vascular invasion. There is alternative option for auto-transplanation of parathyroid gland; delayed autotransplantation of cryopreserved parathyroid tissue or fresh parathyroid tissue are auto-transplantated immediately on operation. The advantages of delayed autotransplantation are potentially autonomous growth and avert the reintroduction of irrepressible hyperplastic tissue and reduce risk to develop recurrent hyperparathyroidism by subsequent follow up. For permanent dialysis patients without any history of aluminum exposure tPTX is also preferred as the risk of permanent hypoparathyroidism and subsequent aluminum bone disease in the persistently uremic state is relatively low. When all parathyroid glands are necessary explore visually, bilateral neck exploration is chosen. Only one parathyroid and side of parathyroid gland is affected, minimally invasive parathyroidectomy can be performed. There are several technique of MIP; radio-guided parathyroidectomy which is least invasive method in which the diseased gland absorbs a small and safe amount of a radioactive material by using special probe. General anesthesia is typically not needed, and the patient can usually return home within a couple of hours. Video-assisted parathyroidectomy is performed by tiny video camera is inserted into a small incision. Locoregional anesthetic is used, rather than general, allowing for a relatively fast recovery time. Endoscopic parathyroidectomy is also performed for minimal scar and high success rate.

Intraoperative parathyroid hormone monitoring. Preoperative localization of all abnormal parathyroid glands is main key for accurate success of parathyroidectomy. However, sometimes the imaging misses the subject due to some facts such as double adenomas, parathyroid hyperplasia, ectopically located gland. To help and know the surgeon decides how much parathyroid gland and tissue to remove and left in the neck, intraopverive parathyroid hormone is monitored. Full-sequence PTH has the shortest half-life compared with other PTH fragments with an average half-life of 2 to 5 minutes. Intraoperative monitoring of PTH concentrations is important because decreases in PTH concentration after gland excision can be one of indication to know successful removal of an adenoma or hyperplasia. Monitoring interval time is not fully understand and fixed yet. But the Irvin/Miami criterion defines a successful decrease in PTH concentration as a decrease of >50% from the higher value of either the pre-incision or pre-excision value, 10 min after the gland has been removed [17]. If the value fails to decrease <50% of the baseline value at 10 min, it may indicate that there are some remaining hypersecreting tissue. Some variations on the method not only require a >50% decrease

from the highest IOPTH concentration at 10 min or 20 min but also a final IOPTH concentration within the reference range [6,9].

Complication and management. Complications of parathyroidectomy are postoperative bleeding and hematoma, recurrent laryngeal nerve injury, hypoparathyroidism and hypocalcemia, persistent or recurrent hyperparathyroidism. The most serious complications are life threatening hematoma which are reported 0.6% [35]. and laryngeal nerve injury which is about 1.1% of patients under thyroid and parathyroid surgery, recovered normal vocal cord within 6 months.[20] Persistent or recurrent hyperparathyroidism is happened in 2% upto 5% patients with primary hyperparathydoism [28]. Mostly It's because of ectopic hyperfunction parathyroid gland, unfounded parathyrpoid gland hyperplasia [5,13].

After operation, patients should be observed for development of cervical hematoma, even though it's rare complication about 0.6%, it is the life threatening complication. Short-term usage of calcium and/or vitamin D supplement would considered after surgery for prophylaxis. The moderate rate of hypocalcemia after parathyroidectomy are reported from 5% to 47% that high rate complications to observed and assessed carefully. The assessment and observation of recovery and complication should require evaluation for at least 6 months. The following laboratory tests include calcium, parathyroid hormone, and 25-hydroxyvitamin D corrected and normalized the level of those parameters by medication and diet. The fully recovery rates for parathryoidectomy should be reached 95% to 99%. The definition of curing is reestablishment of normal calcium homeostasis within minimum 6 months. In case of secondary hyperparathyroidism by hemodialysis, about 27 % of patients after operation are developed 'hungry bone syndrome' which is defined by decrease level of serum total calcium <8.4 mg/dl (2.1 mmol/L) and/or prolonged hypocalcemia for >4 days postparathyroidectomy PTH and use of calcimimetics or vitamin D analogs did not predict hungry bone syndrome[34]. Hungry bone syndrome requires intravenous calcium repletion for an average of 7 days after operation by high doses of oral calcium and vitamin D analog supplementation; calcitriol is the agent of choice given its marked calcemic effects. Serum calcium levels decline to a minimum 3 weeks after surgery and the use of high-calcium dialysate can be considered during this period.

Hypocalcemia can be transient and permanent reported in 05% to 3.8%, which requires life-long treatment. The first step management of hypocalcaemia is starting from day 1 of operation and keeps checking it for at least 3 days during hospitalization. It will be according to individually patient's calcium level (table 7). After parathyroidecomy with severe hyperparathyroidism, if hypocalcaemia less than 2.1mmol/L and prolonged more than 4th day post operation, it's called hungry bone syndrome which is usually associated with skeletal manifestations, and reflected by high preoperative bone turnover, osteitis fibrosa cystica and/or 'brown tumours' [94&&]. Without proper treatment, it would linked to complication of hypocalcemia, which are including seizure, cardiac arrhythmia, severe muscle spasm and cramping, and impaired brain and motor function. The main treatment goal of hungry bone syndrome is replenishing the depleted skeletal calcium stores. It is usually done by calcium supplementation such as calcium gluconate or calcium carbonate and with high dosage of active vitamin D and electrolytes which is insufficiency in current condition for example, magnesium or/and phosphonate. Depending on severe hypocalcemia, the amount calcium supplementation is between 6 to 12g/day. Initially and by severalty, calcium supplement is given intravenously and oral preparation is started as soon as possible with adequate doses of active metabolites vitamin D, which is calcitriol or alfacacidol (2–4μg/day). In case of severe hypocalcemia with symptoms should emergently corrected and treated. Calcium element 100-300 mg (10-30ml of 10% calcium gluconate) diluted in (50-100 mL N/S or dextrose 5% in solution in 10-15' Max: 2 mL/min intravenously. asymptomatic condition with severe hypocalcemia would be corrected by 10 mL of 10% Ca gluconate (100 mL N/S or dextrose 5% in solution) infuse at 100ml/h .Max: 40ml (4g). The calcium solutions for intravenous treatment mush not combine or contain bicarbonate or phosphate because of possibly form calcium salts which are not soluble. The oral daily supplement for treatment of hypocalciema is mainly elemental calcium and vitamin D mediacation. Mostly for elemental calcium is used calcium carbonate which is up to 4g/day and vitamin D for oral treatment is calcitrol and it's up to 4 μg/day [18]. In case of hypocalcemia with significant hypomagnesemia parenteral route treatment can be

used. Up to 50 mmol/day can be administered to patient condition considered by patient's renal function. In hungry bone syndrome, hypomagnesemia is possibly corrected with correction of hypocalcemia [25].

Table 7.

Management of adults with hypocalcemia after surgery

Postoperative day	**Serum tests**	**Therapy**
Night of surgery	Calcium in the evening (approximately 8 PM)	**Ca <1.9** mmol/L**:** Calcitriol 0.5 mcg three times daily x three days and calcium gluconate 3 g/L D5 1/2 normal saline IV at 100 mL/hour
Day 1	Calcium and phosphorus in the morning (approximately 6 AM); if **Ca <1.9** mmol/L, add magnesium	**Ca <1.9** mmol/L**:** Calcitriol 0.5 mcg twice daily x three days and adjust depending upon calcium response and calcium gluconate 3 g/L D5 1/2 normal saline IV at 100 mL/hour and calcium carbonate (1 to 4 g elemental calcium) by mouth daily in divided doses depending upon calcium response **Ca 1.9 to 2.0** mmol/L**:** Calcitriol 0.5 mcg twice daily x three days and adjust depending upon calcium response and calcium carbonate (1 to 4 g elemental calcium) by mouth daily in divided doses depending upon calcium response **Ca >2.0** mmol/L**:** Calcium carbonate (1 g elemental calcium) by mouth twice daily **Mg <2** mg/dL**:** Magnesium sulfate 4 g in 100 mL normal saline IV at 33 mL/hour and magnesium oxide 400 mg by mouth twice daily x one month
Day 2 to 4 more	If day 1 Ca ≤2.0 mmol/L, total calcium and phosphorus	**Ca <1.9** mmol/L **and symptomatic:** Calcitriol 0.25 mcg three times daily and calcium gluconate 3 g/L D5 1/2 normal saline IV at 100 mL/hour and calcium carbonate (1 to 4 g elemental calcium) by mouth daily in divided doses and modify based upon calcium response **Ca <1.9** mmol/L **and asymptomatic:** Calcitriol 0.25 mcg three times daily and calcium carbonate (1 to 4g elemental calcium) by mouth daily in divided doses and modify based upon calcium response **Ca 1.5 to 2.1** mmol/L **or P ≥4.5 mg/dL:** Calcitriol 0.25 mcg daily and calcium carbonate (1 to 4 g elemental calcium) by mouth daily in divided doses and modify based upon calcium response **Ca 2.1 to 2.7** mmol/L **and P ≤4.5 mg/dL:** Calcium carbonate (1 to 4 g elemental calcium) by mouth daily in divided doses and modify based upon calcium response

		Ca ≥2.7 mmol/L**:** No therapy

To correct hypophosphatemia, intravenous phosphate should be avoided because phosphate can joined with calcium to produce more in serum calcium concentration. However severe hypophosphatemia which is lower than 0.31mmol/L is phosphate supplement necessarily. It should be replaced by oral intravenous or intraperitoneal routes in patients on dialysis.

Tertiary hyperparathyroidism. Tertiary hyperparathyroidism refers to autonomous overproduction of PTH with development of hypercalcemia in patients with chronic renal failure and longstanding secondary hyperparathyroidism. Tertiary HPT occurs in the setting of kidney transplantation patient with secondary HPT continue to have increasing PTH level. It is observed in up to 30% of kidney transplant recipient. It also can develop after any long standing period of hypocalcemia such as chronic dialysis or gastrointestinal malabsorption., Long-standing CKD cause several metabolic disturbances that lead to increased secretion of PTH, including hyperphosphatemia, calcitriol deficiency, and hypocalcaemia. Hyperphosphatemia has a direct stimulatory effect on the parathyroid gland cell resulting in nodular hyperplasia and increased PTH secretion. Prolonged hypocalcemia causes hyperplasia of parathyroid chief cell and elevate PTH. After correction of the primary disorder CKD by kidney transplantation, the hypertrophied parathyroid tissue fails to resolute, enlarge over and continues to excessive secretion of PTH, despite withdrawal of calcium and calcitriol treatment even elevated. They also may become resistant to calcimimetic treatment Tertiary HPT is classically caused by hyperplasia of all four glands, though some reports indicate that over 20% of patients may have single or double adenomas as the underlying pathology. Medical treatment is not effected and curative. That's why the primary treatment is surgery, not given oral calcium and phosphate binders since they are typically normocalcemic or hypercalcemic and concurrently hypophosphatemic unlike secondary hyperparathyroidism. Vitamin D supplementation can be used for only delays surgical treatment. The option of surgical procedure is tPTX+AT, tPTX,sPTX and limited parathyroidectomy as well as similar one for secondary hyperparathyroidism. Surgical complications are rare and it's safe and choice of treatment.

References:

1. Bleyer AJ, Burke SK, Dillon M, Garrett B, Kant KS, Lynch D, Rahman SN, Schoenfeld P, Teitelbaum I, Zeig S, Slatopolsky E: A comparison of the calcium-free phosphate binder sevelamer hydrochloride with calcium acetate in the treatment of hyperphosphatemia in hemodialysis patients. Am J Kidney Dis 33: 694–701, 1999
2. Block GA, Martin KJ, de Francisco AL, et al. Cinacalcet for secondary hyperparathyroidism in patients receiving hemodialysis. N Engl J Med. 2004;350:1516–1525.
3. Brown AJ, Dusso AS, Slatopolsky E: Vitamin D analogues for secondary hyperparathyroidism. Nephrol Dial Transplant 17: 10–19, 2002
4. Chang CY, Rosenthal DI, Mitchell DM, Handa A, Kattapuram SV, Huang AJ. Imaging Findings of Metabolic Bone Disease. Radiographics. 2016 Oct;36(6):1871-1887. [PubMed]
5. Chen H, Wang TS, Yen TW, Doffek K, Krzywda E, Schaefer S, Sippel RS, Wilson SD. Operative failures after parathyroidectomy for hyperparathyroidism: the influence of surgical volume. Ann Surg. 2010 Oct;252(4):691-5.
6. Chiu B , Sturgeon C , Angelos P . Which intraoperative parathyroid hormone assay criterion best predicts operative success? A study of 352 consecutive patients. Arch Surg 2006;141:483–8.
7. Colloton M, Shatzen E, Miller G, Stehman-Breen C, Wada M, Lacey D, Martin D: Cinacalcet HCl attenuates parathyroid hyperplasia in a rat model of secondary hyperparathyroidism. Kidney Int 67: 467–476, 2005
8. Cozzolino M, Tomlinson J, Walsh L, Bellasi A. Emerging drugs for secondary hyperparathyroidism. Expert Opin Emerg Drugs. 2015;20(2):197–208.

9. Di Stasio E , Carrozza C , Pio Lombardi C , Raffaelli M , Traini E , Bellantone R , Zuppi C . Parathyroidectomy monitored by intra-operative PTH: the relevance of the 20 min end-point. Clin Biochem 2007;40:595–603.
10. El-Kishawi AM, El-Nahas AM. Renal osteodystrophy: review of the disease and its treatment. Saudi J Kidney Dis Transpl. 2006 Sep;17(3):373-82. [PubMed]
11. Galassi A, Cupisti A, Santoro A, Cozzolino M. Phosphate balance in ESRD: diet, dialysis and binders against the low evident masked pool. J Nephrol. 2015;28:415–429.
12. Galitzer H, Lavi-Moshayoff V, Nechama M, Meir T, Silver J, Naveh-Many T: The calcium-sensing receptor regulates parathyroid hormone gene expression in transfected HEK293 cells. BMC Biol 7: 17, 2009
13. Gough I. Reoperative parathyroid surgery: the importance of ectopic location and multigland disease. ANZ J Surg. 2006 Dec;76(12):1048-50.
14. Goyal A, Anastasopoulou C, Ngu M, Singh S. StatPearls [Internet]. StatPearls Publishing; Treasure Island (FL): Aug 8, 2021. Hypocalcemia.
15. Guidelines by the Japanese Society for Dialysis Therapy 2017
16. Hans SK, Levine SN. StatPearls [Internet]. StatPearls Publishing; Treasure Island (FL): Jul 18, 2021. Hypoparathyroidism
17. Irvin GL , Deriso GT . A new, practical intraoperative parathyroid hormone assay. Am J Surg 1994;168:466–8.
18. Illustrated Anatomy of the Head and Neck, Fehrenbach and Herring, Elsevier, 2012, p. 159
19. JANCAR J. RICKETS WITH SECONDARY HYPERPARATHYROIDISM IN A SEVERELY SUBNORMAL CHILD. Arch Dis Child. 1963 Aug;38(200):412-4. [PMC free article] [PubMed]
20. Joliat GR, Guarnero V, Demartines N, Schweizer V, Matter M. Recurrent laryngeal nerve injury after thyroid and parathyroid surgery: Incidence and postoperative evolution assessment. Medicine (Baltimore). 2017 Apr;96(17):e6674.
21. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Kidney Int Suppl. 2009;(113):S1–S130.
22. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Update Work Group. KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Kidney Int Suppl (2011). 2017 Jul;7(1):1-59. [PMC free article] [PubMed]
23. Komaba H, Nakanishi S, Fujimori A, Tanaka M, Shin J, Shibuya K, Nishioka M, Hasegawa H, Kurosawa T, Fukagawa M: Cinacalcet effectively reduces parathyroid hormone secretion and gland volume regardless of pretreatment gland size in patients with secondary hyperparathyroidism. Clin J Am Soc Nephrol 5: 2305–2314, 2010
24. Lacativa PG, Franco FM, Pimentel JR, Patrício Filho PJ, Gonçalves MD, Farias ML. Prevalence of radiological findings among cases of severe secondary hyperparathyroidism. Sao Paulo Med J. 2009 May;127(2):71-7. [PubMed]
25. Lappas D, Noussios G, Anagnostis P, Adamidou F, Chatzigeorgiou A, Skandalakis P (September 2012). "Location, number and morphology of parathyroid glands: results from a large anatomical series". Anat Sci Int. 87 (3): 160–4. doi:10.1007/s12565-012-0142-1. PMID 22689148. S2CID 207431255
26. Lau, WL; Obi, Y; Kalantar-Zadeh, K (7 June 2018). "Parathyroidectomy in the Management of Secondary Hyperparathyroidism". Clinical Journal of the American Society of Nephrology. 13 (6): 952–961. doi:10.2215/CJN.10390917
27. Llach F, Fernández E. Overview of renal bone disease: causes of treatment failure, clinical observations, the changing pattern of bone lesions, and future therapeutic approach. Kidney Int Suppl. 2003 Nov;(87):S113-9. [PubMed]

28. Mazotas IG, Yen TWF, Doffek K, Shaker JL, Carr AA, Evans DB, Wang TS. Persistent/Recurrent Primary Hyperparathyroidism: Does the Number of Abnormal Glands Play a Role? J Surg Res. 2020 Feb;246:335-341
29. Moe SM, Cunningham J, Bommer J, Adler S, Rosansky SJ, Urena-Torres P, Albizem MB, Guo MD, Zani VJ, Goodman WG, Sprague SM: Long-term treatment of secondary hyperparathyroidism with the calcimimetic cinacalcet HCl. Nephrol Dial Transplant 20: 2186–2193, 2005
30. Oprisiu R, Hottelart C, Ghitsu S, Said S, Westeel PF, Morinière P, el Esper N, Pruna A, Fournier A. [Renal osteodystrophy (1): invasive and non-invasive diagnosis of its pathologic varieties]. Nephrologie. 2000;21(5):229-37. [PubMed]
31. Patel SR, Ke HQ, Vanholder R, Koenig RJ, Hsu CH: Inhibition of calcitriol receptor binding to vitamin D response elements by uremic toxins. J Clin Invest 96: 50–59, 199
32. Parathyroid surgery: Recovery, The American Association of Endocrine Surgeons
33. Robbins and Cotran pathologic basis of disease. Kumar, Vinay, 1944-, Abbas, Abul K.,, Aster, Jon C.,, Perkins, James A. (Ninth ed.). Philadelphia, PA. 2014.
34. Risk factors and clinical course of hungry bone syndrome after total parathyroidectomy in dialysis patients with secondary hyperparathyroidism. Ho LY, Wong PN, Sin HK, Wong YY, Lo KC, Chan SF, Lo MW, Lo KY, Mak SK, Wong AKBMC Nephrol. 2017 Jan 10; 18(1):12.
35. Rosenbaum MA, Haridas M, McHenry CR. Life-threatening neck hematoma complicating thyroid and parathyroid surgery. Am J Surg. 2008 Mar;195(3):339-43; discussion 343.
36. Sekercioglu N, Angeliki Veroniki A, Thabane L, et al. Effects of different phosphate lowering strategies in patients with CKD on laboratory outcomes: a systematic review and NMA. PLoS One. 2017;12(3):e0171028.
37. Slatopolsky E, Brown A, Dusso A: Pathogenesis of secondary hyperparathyroidism. Kidney Int Suppl 73: S14–S19, 1999
38. Schlosser K, Veit JA, Witte S, et al. Comparison of total parathyroidectomy without autotransplantation and without thymectomy versus total parathyroidectomy with autotransplantation and with thymectomy for secondary hyperparathyroidism: TOPAR PILOT-Trial. Trials 2007;8:22
39. The Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines 2007
40. Wilkieson TJ, Rahman MO, Gangji AS, Voss M, Ingram AJ, Ranganath N, Goldsmith CH, Kotsamanes CZ, Crowther MA, Rabbat CG, Clase CM. Coronary artery calcification, cardiovascular events, and death: a prospective cohort study of incident patients on hemodialysis. Can J Kidney Health Dis. 2015;2:29. [PMC free article] [PubMed]

ISSN 2181-3426

Journal DOI: 10.26739/2181-3426

MARKAZIY OSIYO ENDOKRINOLOGIK JURNALI

3 ЖИЛД, 2 СОН

ЦЕНТРАЛЬНО АЗИАТСКИЙ ЭНДОКРИНОЛОГИЧЕСКИЙ ЖУРНАЛ

ТОМ 3, НОМЕР 2

CENTRAL ASIAN ENDOCRINOLOGICAL JOURNAL

VOLUME 3, ISSUE 2

Editorial staff of the journals of www.tadqiqot.uz
Tadqiqot LLC the city of Tashkent,
Amir Temur Street pr.1, House 2.
Web: http://www.tadqiqot.uz/; Email: info@tadqiqot.uz
Phone: (+998-94) 404-0000

Контакт редакций журналов. www.tadqiqot.uz
ООО Tadqiqot город Ташкент,
улица Амира Темура пр.1, дом-2.
Web: http://www.tadqiqot.uz/; Email: info@tadqiqot.uz
Тел: (+998-94) 404-0000