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REVIEW ARTICLE

Parathyroidectomy for dialysis patients in the era of calcimimetics: The surgeons' point of view

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Abstract: *Calcimimetics* is a new drug for lowering serum parathyroid hormone (PTH), calcium and phosphate in patients with hyperparathyroidism (HPT) on long-term dialysis. It became available on market in 2006. The impact of calcimimetics on the treatment by parathyroidectomy (PTx) was reviewed from the surgeons' point of view. Cure of renal HPT by calcimimetics is not feasible, but calcimimetics can improve preoperative cardiac ventricle ejection fractions by lowering serum PTH. Heart failure is not necessarily a contraindication for PTx. PTx should be done before irreversible organ damage occurs. Limb gangrenes is an ominous sign and should be prevented by frequent checkup for peripheral arterial circulation. The impact of renal osteodystrophy on the quality of life and as indirect cause of mortality deserves more attention in patients with renal HPT. Delayed referral to PTx leads to more complicated patients. A consensus between nephrologists and surgeons about propitious timing for PTx is necessary. Future prospect on the surgical treatment of renal HPT is proposed.
Supplemental figure; http://links.lww.com/ASAIO/A782

Keywords: Calcimimetic agents; Hyperparathyroidism; Parathyroidectomy

1. INTRODUCTION

End stage renal disease (ESRD) is the most common cause of secondary hyperparathyroidism (HPT). Decreased synthesis of active vitamin D and phosphate retention lead to chronic hypocalcemia and parathyroid hormone (PTH) hypersecretion from the stimulated parathyroid glands. Hemodialysis or peritoneal dialysis is the most effective treatment for ESRD unless a renal transplantation is available. However, complications, such as osteodystrophy, and soft tissue calcifications, may occur during long-term dialysis. Parathyroidectomy (PTx) is needed if renal HPT persists and is refractory to medical treatments. Otherwise, patients may die from complications of cardiovascular disease or become bedridden from pathologic fractures. Recent progress in medical treatments using phosphate binding agents and calcimimetics had greatly improved the quality of life for the dialysis patients. This article is to review the impact of calcimimetics on the surgical treatment of renal HPT from the surgeons' perspective.

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Calcimimetics works through modulation of parathyroid calcium sensing receptors. It was approved by US Food and Drug Administration in 2003 and became commercially available in 2006. Since then, it was widely used in the medical management of renal HPT patients in Europe, Japan, North America, and other countries.[1,2] The annual prescribing cost of calcimimetics is at least 260 million dollars in the United States.[3] It had dramatically reduced the number of patients with renal HPT referred for PTx,[1] especially in Japan. Calcimimetics lower serum PTH by 40% to 50%, require continuing long-term use and are expensive. It is, therefore, not equivalent to PTx.[4] In a cost utility analysis, at 7.25 months, the medical expense of calcimimetics becomes higher than that of PTx. The EVOLVE trial and Cochran review had concluded that[5,6] calcimimetics did not reduce the risk of death and cardiovascular events and may be beneficial to a few patients with contraindication for operations. Moreover, a 2 years delay in treatment with continuously elevated preoperative serum PTH was observed.[7] Once parathyroid nodular hyperplasia developed, it is more refractory to calcimimetics therapy.[8]

Currently, about 25% of patients with renal HPT still need PTx.

2. INDICATIONS

Symptoms and signs of bone pain, skin itching, soft tissue calcification, and muscle weakness are classical indications of PTx for patients with renal HPT. Patients refractory to medical treatment or cannot afford long-term expensive medications also need PTx.[9,10] There are no international guidelines using serum PTH levels as an indication for PTx in patients with renal HPT. In Japan and the United States, serum PTH >500 pg/mL[11] and >800 pg/mL,[12] respectively, as well as patients refractory to medical treatment are indications. In Taiwan, almost all patients have serum PTH >1100 pg/mL when referred for PTx (Fig. 1). Therefore, it is difficult to compare outcomes among published series.

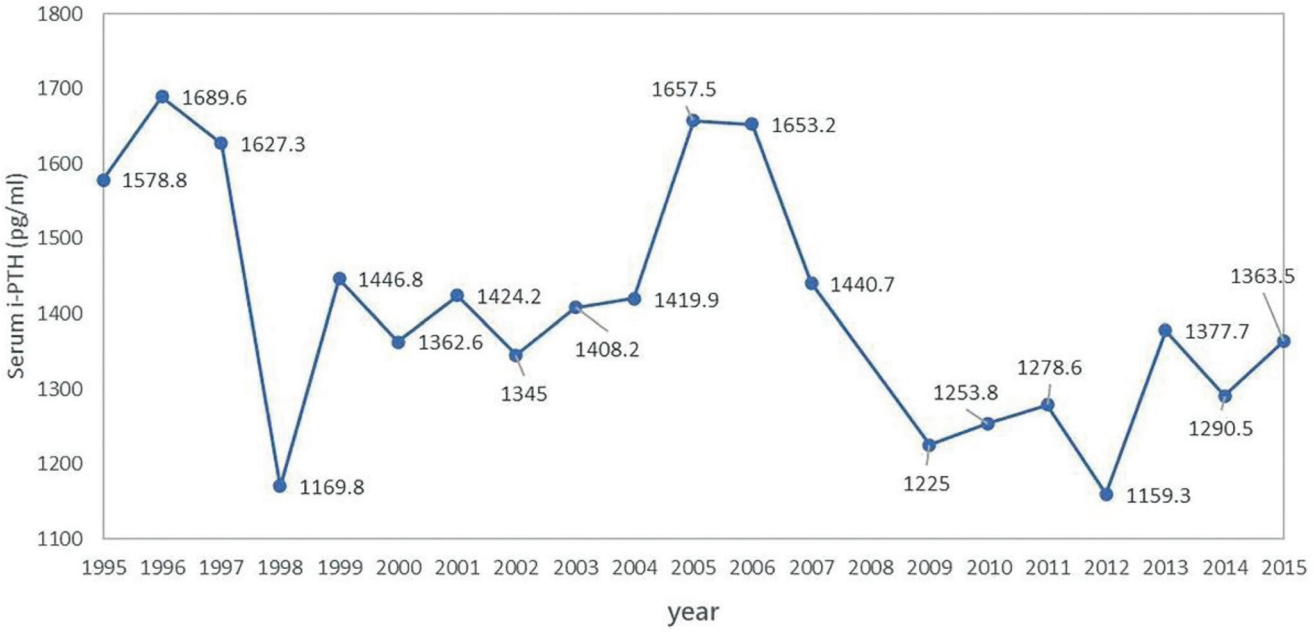

Fig. 1 Average serum i-PTH levels before parathyroidectomy from 1995 to 2015 (CJ Hung, unpublished data). PTH = parathyroid hormone.

We use combined laboratory findings and symptoms and signs as indications for PTx: (1) serum PTH >800 pg/mL with enlarged parathyroid glands, (2) serum PTH <800 pg/mL with either calcium × phosphate product >55 mg^2/dL^2, or serum calcium alone >11 mg/dL, or phosphate >6 mg/dL, and with soft tissue calcification, or renal osteodystrophy (Table 1).

3. CLINICAL MANIFESTATIONS

3.1. Tissue calcification

Tissue calcification occurs when serum calcium and phosphate product is over the solubility product. Because of hyperactivity of osteoclasts in renal HPT, the calcium and phosphate instead of depositing into the skeleton deposit in extraskeletal tissues, such as cornea, periarticular soft tissue, vascular wall, and visceral organs (Fig. 2).

3.1.1. Periarticular soft tissue calcification

Periarticular soft tissue calcification is commonly seen at large joints, such as shoulder, hip, elbow, and causes pain with limitation of its range of motion. Nerve compression causes neuropathy. Occasionally, calcification of the intervertebral facet ligaments may lead to ankylosis and deformity of spine. Hyperextension and flexion of the neck is impaired if cervical spine ankylosis is severe.

Table 1

A combined laboratory and symptoms/ signs indication for parathyroidectomy in renal hyperparathyroidism proposed by the authors

Serum PTH > 800 pg/mL with enlarged glands	
Serum PTH < 800 pg/mL but	Ca > 11 mg/dL or P > 6 mg/dL Ca × P > 60 mg^2/dL^2 with evidence of soft tissue calcification Alk-P > 100 U/L with bone pain and evidence of osteoporosis

PTH = parathyroid hormone.

3.1.2. Vascular calcification

Vascular calcification is common but not pathognomonic of renal HPT. It also occurs in diabetes and atherosclerosis. It is not known if patients with renal HPT secondary to diabetic nephropathy have higher risk of arterial wall calcification because of dual mechanism working in concert. More often, calcification occurs in aorta, iliac, and mesenteric arteries. Calcification of limb arteries causes peripheral arterial occlusive disease, and may result in gangrene, as it is seen in diabetic feet. Occasionally, calcification of penile arteries is visible on plain films and is probably related to erectile dysfunction.

3.1.3. Visceral calcification

Visceral calcification is rare, nowadays. Earlier reports show, it occurred in lung, liver, mesentery, and heart. Pathology and pathophysiology of calcification of the heart is best known. Calcification of the cardiac valves and conduction system lead to valvular stenosis and regurgitation, and electrophysiologic disorder. These mechanical and electrophysiologic disorders may coexist and progress with disease.

> Thirty years ago, the authors took care of a dialysis patient with "cotton ball" lesion of the lung, suspected to be lung cancer with repeated negative cytology by bronchial lavage. The diagnosis of renal hyperparathyroidism with lung calcification was delayed at local hospital until patients was referred to this medical center. Within a few days, he developed progressive 1st degree, 2nd degree then complete AV block, and asystole, refractory to cardiac pacing; and died.[13]

3.2. Renal osteodystrophy

Osteopenia or osteoporosis is a common manifestation of mineral and bone disorder in ESRD and can be asymptomatic

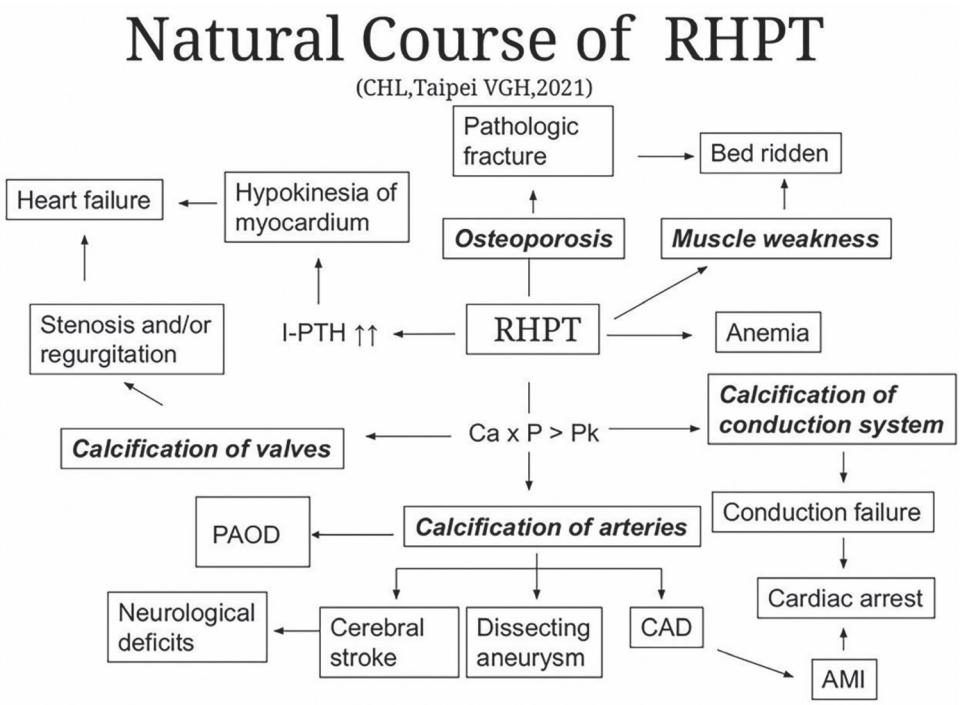

Fig. 2 Natural course of renal hyperparathyroidism. It illustrates the possible developing mechanism of various complications of renal hyperparathyroidism. Heart failure may be caused by hypokinesia of myocardium, or calcification of cardiac valves, coronary arteries, as well as conduction systems. AMI = acute myocardial infarction; CAD = coronary arterial disease; PAOD = peripheral arterial occlusive disease; RHPT = renal hyperparathyroidism.

until advanced stage. It is the most common cause of pathologic fractures in the vertebrae, the forearm, and the hip, either spontaneous or with minor stress. Compression fracture of the vertebrae leads to kyphosis, scoliosis or kypho-scoliosis, and shortening of body height (Fig. 3). Deformity of the chest can affect pulmonary function. Muscle weakness in renal HPT often accompanies with unstable gaits, and increasing the risk of falls and fracture of weight bearing bone. Because of abnormal bone mineral metabolism in renal HPT, patients may have delayed bone healing or even nonunion of broken bones. Many patients become chronically bedridden, and complications such as pneumonia, urinary tract infection, and bed sores ensue. Quality of life is compromised and can be an indirect cause of death in patients with renal HPT.

3.3. Calciphylaxis

Calciphylaxis is a catastrophic illness due to extensive peripheral vascular calcification with compromised peripheral micro-circulation. It leads to rapid progressive skin and muscle necrosis, fever, hypotension, myocardial, mesenteric vascular occlusion and functional disturbance of central nervous system. It is a true emergency for PTx with mortality rate of 50% to 80%.[14]

4. SURGICAL TREATMENT

4.1. Preoperative assessment and preparations

Before operation, image studies such as 99 m Tc sestamibi scan and ultrasound is not very helpful for localization of all parathyroid glands.[15] Usually, they visualize only 1 or 2 dominant glands. However, preoperative neck ultrasound is helpful to detect any concurrent thyroid nodules or cancers.[16] A bone mineral density test and serum alkaline phosphatase levels may help to predict postoperative hypocalcemia from bone hunger. Preoperative assessment of cardiac function is very important,[17] as listed in Table 1. Occasionally, we use hyperbaric oxygen therapy for those with compromised peripheral circulation of the limbs to improve blood oxygenation. The effectiveness is not proven.

4.2. Operation models

Endoscopic or remote access PTx have been tried but not routinely used.[18] Four glands exploration through a cervical incision is the standard approach. . Subtotal PTx resecting 3½ parathyroid glands, or total PTx with autotransplantation are the operations most frequently performed.[19,20] Subtotal PTx is more popular in North America. It has the advantage of less severe postoperative hypocalcemia, but with disadvantage of recurrence. As chronic renal failure continues without transplantation the parathyroid remnant continues to grow and has a recurrence rate as high as 32.1%.[21] Total PTx with autotransplantation of about 100 mg of parathyroid tissue in the abdominal or forearm muscle, or subcutaneously is popular in Europe, Japan, and other Asian countries. It has a lower rate of recurrence (8–10%),[22] but a higher rate of postoperative hypocalcemia. In case of recurrence, excision of the graft can be done under local anesthesia instead of a reoperative transcervical PTx. Mortality and morbidity do not differ significantly between subtotal PTx and total PTx with autotransplantation. Neither technique appears to provide superior outcomes. We prefer a subtotal PTx in patients with severe osteoporosis and high serum levels of alkaline phosphatase because bone hunger in a patient after total PTx may lead to extreme hypocalcemia before the grafted parathyroids start to function, which takes a few days to weeks. Extreme hypocalcemia may cause coma, seizure, and cardiac arrest. A serum calcium <1.9 mmol/L(or 7.6 mg/dL) is potentially life threatening.[23] Total PTx with autotransplantation is not recommended for patients on waiting list of kidney transplantation because of the higher risk of a-parathyroid state and severe hypocalcemia. Parathyroid graft survival is not 100%,

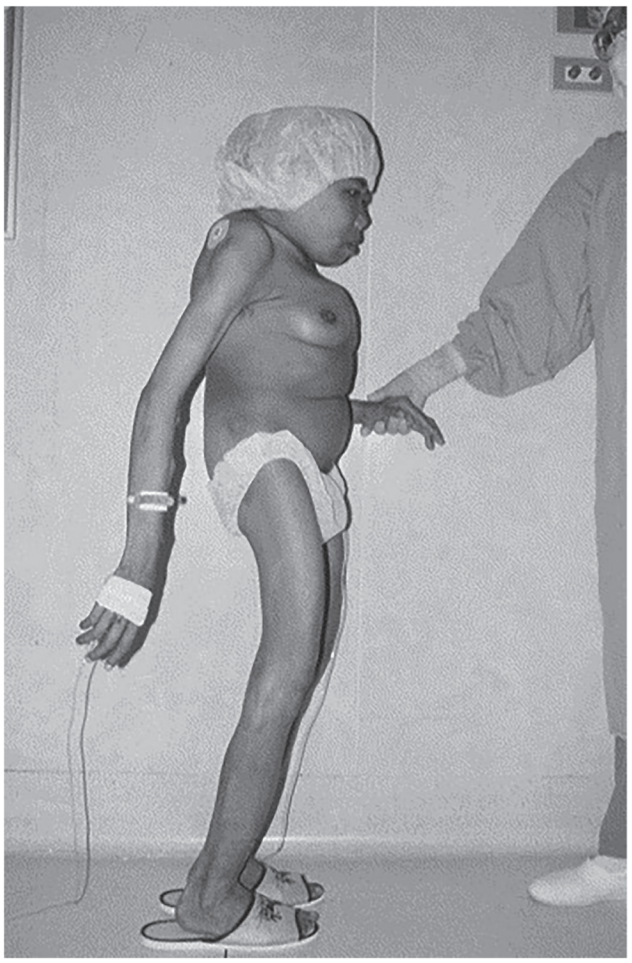

Fig. 3 A case of renal hyperparathyroidism with severe cervical spine ankylosis and kypho-scoliosis.

especially if only cryopreserved parathyroid is used. In subtotal PTx, if all 4 glands are remarkably enlarged with nodular hyperplasia, it may be difficult to find less nodular part for remnant. We recommend leaving about 100 to 200 mg, instead of a larger 1/2 gland parathyroid remnant to avoid early recurrence. Total PTx without autotransplantation[24,25] offers lowest rate of recurrence (2–4%) and allows for adequate vitamin D supplementation. The recurrence of renal HPT after a total PTx is probably due to growth of residual microscopic parathyroid tests.[26] Total PTx without autotransplantation is for noncandidates of kidney transplantation. It is not recommended in guidelines because of the risk of adynamic osteodystrophy. A recent study showing improvement in BMD in lumbar spine and hip after total PTx needs to be confirmed.[27] For comparison, the three models of PTx was listed in Table 2.

4.3. Postoperative care

For those with preoperative high serum levels of alkaline phosphatase and image evidence of severe osteoporosis, postoperative hypocalcemia is anticipated. After operation, serum calcium should be checked on the operation day and replace calcium as needed because bone hunger may occur very early. Occasionally, the patients need intensive calcium replacement and more frequent serum calcium measurement in a day. Hemodialysis with high calcium dialysate is helpful, but laborious. It occurred more frequently after a total PTx.[28]

4.4. Postoperative outcomes

In general, quality of life improves after a successful PTx.[29,30] Japanese study showed PTx reduced cardiovascular death[31] and increased cardiac ejection fraction.[32] Big data analysis from Taiwan National Health Insurance Program showed reduced risk of acute coronary events, and cerebral stroke, as well as peripheral arterial occlusive disease.[33–35]

After PTx, skin itching and bone pain may be relieved immediately,[36] osteoporosis and muscle weakness may improve but takes time.[37,38] Soft tissue calcifications may resolve. Risk of hip fracture is reduced,[39,40] but compression fracture of spine does not recover. Gangrene of extremities is irreversible, and usually result in autoamputation, or sepsis requiring amputation for life saving. The recovery of damaged visceral organs remains a challenge. Thus, Tominaga advised early PTx for better outcomes. The average serum PTH levels at PTx was much lower after 1998 than before in his monograph.[32] The 2012, Japanese Society for Dialysis Therapy guidelines recommended PTx when patients' serum PTH is >500 pg/mL or less with concurrent refractory hypercalcemia or hyperphosphatemia. This may be one of the reasons why the Japanese dialysis patients had better survival rates than those in Taiwan and other countries.[41–43]

4.5. Recurrence

Recurrent renal HPT can be due to hyperfunction of parathyroid remnant, or graft, or supranumerary parathyroid glands after either subtotal PTx or total PTx with autotransplantation.[44] Rarely, parathyromatosis can occur due to intraoperative tissue seeding, growth, and proliferation from a ruptured parathyroid.[45] Subsequent en bloc surgical removal is laborious and risky.[46] It is important to keep the parathyroid capsule intact during initial PTx.

4.6. Limitations

Although PTx is an effective treatment for renal HPT, it is not without contraindications and limitations.

Limitations include

1. Unlocalized recurrent renal HPT: Recurrent renal HPT due to missed glands or supernumerary glands is a challenge for reoperations. Without accurate localization, reoperative PTx by blind neck exploration is dangerous, and frequently leads to more complications.
2. Deep seated mediastinal parathyroid if sternotomy is needed: Upper mediastinal hyperplastic parathyroid glands can

Table 2

A comparison of three models of parathyroidectomy for renal hyperparathyroidism

Results Operation models	Subtotal parathyroidectomy	Total parathyroidectomy with autotransplantation	Total parathyroidectomy without autotransplantation
Postoperative hypocalcemia	Lower rate	Higher rate	Much higher rate
Recurrent hyperparathyroidism	As high as 32.1%	8–10%	2–4%
Management on recurrence	Neck re-exploration	Local excision for hypertrophic graft or neck re-exploration if supernumerary glands found	Neck re-exploration if supernumerary glands found

Table 3

Cardiac LVEF improvement after 7 weeks use of calcimimetics in a 60-year-old male with renal hyperparathyroidism before he had a safe 2 glands PTx

	Cinacalcet ↓		2 gland PTx (4/11) ↓
Date	2/20	4/9	5/15
Data			
i-PTH	4032	2201	2309
LVEF	28%	36%	42%

LVEF = left ventricle ejection fraction; PTH = parathyroid hormone; PTx = parathyroidectomy.

usually be removed transcervically. However, if the target lesion is deep and near great vessels and difficult for thoracoscopy, a sternotomy is needed. Postoperative nonunion of sternum can be a problem because of osteoporosis in these patients.

3. Cervical spine ankylosis: Cervical spine ankylosis can limit neck hyperextension and make exploring upper parathyroid glands difficult. Recently developed transoral endoscopic PTx technique may be an alternative but needs verification. Otherwise, a radio-guided or image-guided parathyroid ablation may be helpful if the target diseased gland can be localized.
4. Uncorrectable bleeding tendency.
5. Severe respiratory muscle wasting: Muscle wasting is more frequently seen in lower limbs. Some patients, however, may have severe muscle wasting including upper limbs and intercostal muscles. It may result in difficult respirator weaning after general anesthesia. This can be screened preoperatively by the performance of self hair-combing, as well as respiratory function test.

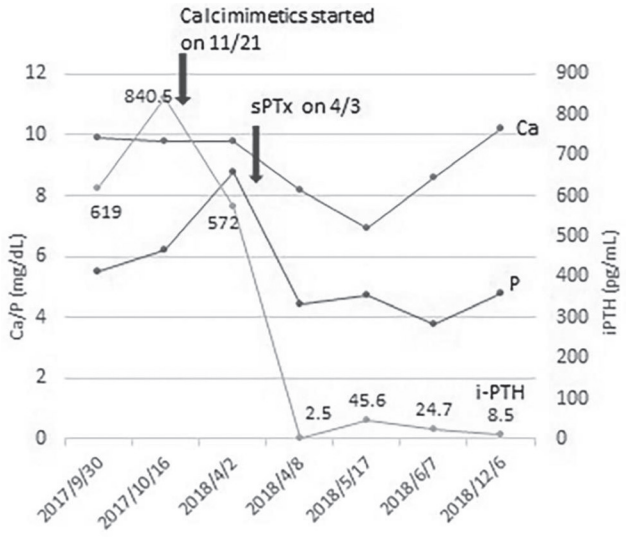

Fig. 4 An illustration of preparathyroidectomy and post-parathyroidectomy serum calcium, phosphate, and PTH in a 60-year-old male RHPT patient with toe gangrene and sepsis. He had cardiac triple vessel calcification despite prior coronary arterial by-pass. After intensive care and calcimimetics for 5 months, his serum i-PTH was lowered, LVEF was improved from 27% to 32% and LBBB disappeared. A 3 glands and 80% sPTx was done leaving about 100 mg remnant intact. Pathology showed all nodular hyperplasia. Eight months after PTx, he was still alive, but with autoamputation of dry gangrenous feet. Two years later, he died of multiple organ failure after an episode of upper respiratory tract infection and pneumonia without evidence of recurrent renal hyperparathyroidism. LBBB = left bundle branch block; LVEF = left ventricle ejection fraction; PTH = parathyroid hormone; PTx = parathyroidectomy; RHPT = renal hyperparathyroidism.

5. CONTRAINDICATIONS

Sepsis, multiple organ failure, poor risk for anesthesia, coexistent uncontrollable malignant disease, as well as extremely old and frail patients are considered as contraindications of PTx for renal HPT. Poor prognosis of coexistent diseases, intolerance of operation, and unfavorable life expectancy are major concerns.

5.1. Heart failure may not be a contraindication for parathyroidectomy

Heart failure in patients with renal HPT may be due to pumping failure or conduction failure, or both. Pumping failure is caused by calcification of coronary arteries, myocardium, and cardiac valves. In addition, extreme high serum PTH may cause hypokinesis of myocardium. Cardiac functions should be assessed and deficits treated before PTx. Conduction failure is due to calcification of conduction fibers.[47] Calcimimetics treatment lowers serum PTH and may improve cardiac function, and improve safety during PTx (Table 3). Perhaps, calcimimetics are helpful to improve myocardial contractility for those coronary arterial disease and valvular dysfunction are not, but high serum PTH is the major cause of cardiac dysfunction, and could be useful for pre-PTx preparation. Further studies are needed for documentation. At present time, we prefer treating with calcimimetics in patients with extremely high serum PTH and low cardiac ejection fractions even after coronary intervention for a few weeks before PTx (Fig. 4).

6. CONCLUSION

The impact of renal osteodystrophy on the quality of life and as indirect cause of mortality deserves more attention in patients with renal HPT. Calcimimetics treatment is not a definitive treatment for renal HPT but can improve the cardiac ejection fraction for high risk patients before PTx. PTx is less expensive than long-term calcimimetics treatment for management of renal HPT. PTx reduces incidences of acute coronary diseases, cerebral strokes, peripheral arterial occlusive disease, and hip fracture. It relieves symptoms of skin itching and bone pain, and resolves soft tissue calcification. Early PTx should be considered before occurrence of irreversible organ damage with reduced functional reserve. Limb gangrenes should be prevented by frequent examination of peripheral arterial circulation. Delayed referral leads to more complicated patients. Consensus between nephrologists and surgeons for optimal timing of PTx is necessary.

7. FUTURE PROSPECT

Since renal HPT is not a homogenous disease entity, patient outcome is affected by the underlying systemic disease of renal failure, such as diabetes. It is necessary to investigate the difference between the diabetic and nondiabetic patients. The potential advantage of total PTx without autotransplantation in selected patients needs further study. In patients with adynamic osteodystrophy after a total PTx, intermittent PTH treatment may be economically feasible. Optimal remnant size for subtotal PTx and optimum postoperative serum PTH level require more studies. After a successful PTx, recurrence is unavoidable as long as the patient remains on dialysis. Different patient may need different parathyroid function provided from different size of remnant or graft.

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