Secondary hyperparathyroidism in chronic kidney disease – recent paradigm shift in clinical management

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Introduction

Primary hyperparathyroidism is not a very common condition but is well known to doctors and medical students. The increased parathyroid hormone (PTH) secretion causes hypercalcaemia with clinical manifestations of bone resorption, urinary stones and abdominal pain ('bones, stones and abdominal groans'). On the other hand, secondary hyperparathyroidism (SHPT) in renal failure patients is much more prevalent but its clinical effects were not well elucidated until recently.

A few decades ago, patients with end-stage renal failure or chronic kidney disease (CKD) stage 5 did not survive long. With the development of long-term dialysis, such patients can be maintained on dialysis with a good quality of life. These patients form a 'window' for SHPT to be studied. Over the years, considerable advances were made in the understanding of the clinical and patho-physiology of SHPT. This led to the discovery of new medications and a paradigm shift in its management. In retrospect, the era of the 90's was a 'watershed' and the authors would like to share their experiences over the past 30 years in this field.

Before the 1980's

In the early 1970's, Hector DeLuca made the landmark discovery that the native vitamin D (cholecalciferol) has to be converted in the liver to 25 hydroxy-vitamin D and then to 1,25 dihydroxy-vitamin D3 (calcitriol), the active hormone, in the kidneys. The 1-alpha-hydroxylase in the kidneys performs the 1-alpha-hydroxylation step. The decreased ability for renal hydroxylation in renal failure is due to 1-alpha-hydroxylase deficiency.

In renal failure, the serum calcium tended to be low as the failing kidneys could not produce enough active vitamin D through renal conversion, resulting in impaired calcium in the gut. Another cause was the phosphate retention due to decreased filtration and excretion of the phosphate load. Serum phosphate retention led to hypocalcaemia. As a result of the hypocalcaemia, the parathyroid glands were stimulated with increased secretions of PTH. The SHPT caused the restoration of serum calcium by mobilization of calcium from the bones to the blood stream. It also has some phosphaturic effect with partial correction of the hyperphosphataemia. In summary, SHPT is a biological adaptation to restore normal blood calcium levels at the expense of increased serum PTH. This is physiological as the serum calcium has a lot of biological effects in the body and its blood level has to be maintained within a very narrow range.

In SHPT, the PTH is increased and this can be detected by PTH essay. In the 1970's, it was not widely available and indirect tests such as radiological changes, serum calcium and alkaline phosphatase were used. There was also some uncertainly as to which PTH essay should be used in patients with renal failure: the N-terminal essay, C-terminal assay or the intact PTH (iPTH) assay. The commonest pathology caused by SHPT is osteitis fibrosa cystica with bone resorption. It could be detected by X-ray which showed the 'miliary' bone resorption of the skull ('pepper-pot' skull), sub-periosteal erosion of the distal phalanges and the 'rugger jersey spine' (bone sclerosis on the upper and lower margins of the vertebrae). (Figures 1 to 3). Bone X-rays were readily available in the 1970's but radiological changes occur late in the process of the disease. Bone biopsy was much more accurate in the investigation of renal osteodystrophy but it was more invasive (Figure 4).

Treatment

Since active vitamin D3 was available in the 1970's it was given to renal failure patients for treatment. The active vitamin Ds used included 1,25 dihydroxycholecaliferol (calcitriol) or 1-alpha-cholecalciferol. Upon administration of the drug, the vitamin D deficiency was corrected and

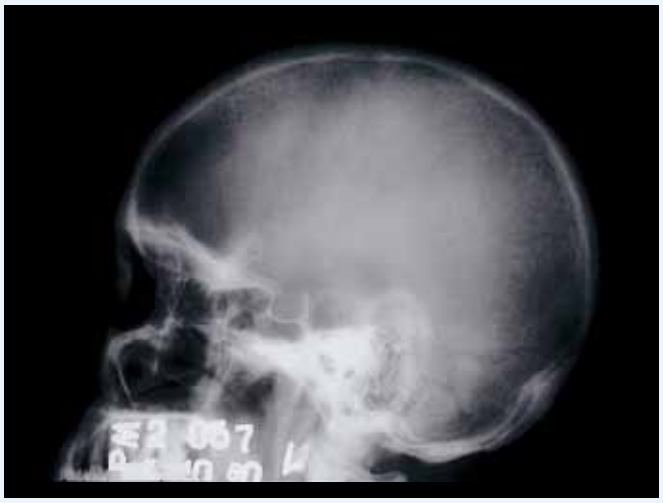


Figure 1. SHPT: The pepper-pot skull.

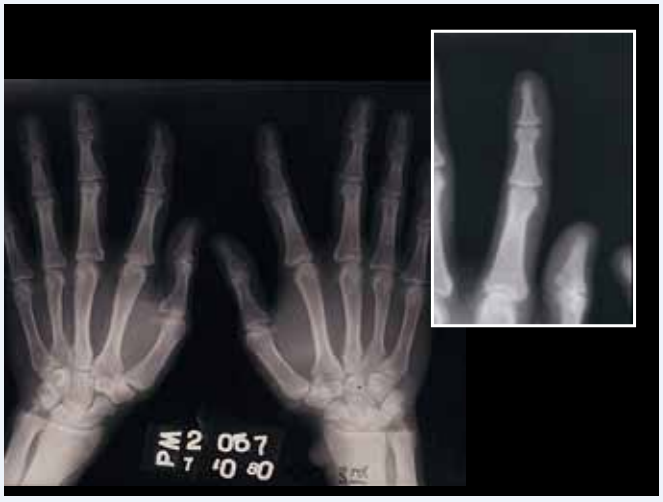


Figure 2. SHPT: The subperiosteal absorption of the distal phalanges.

with it, the correction of the hypocalcaemia and suppression of the SHPT.

One of the drawbacks of calcitriol administration was the development of hypercalcaemia and hence calcium levels would need to be checked frequently. Overdose of the calcitriol caused vascular calcification with many detrimental effects. Fortunately, calcitriol has a short biological half-life and the serum calcium levels fall quickly on stopping the medicine.

If the SHPT could not be adequately controlled despite medical therapy, surgical hyperparathyroidectomy was performed. One practice was to have all the four parathyroid glands removed and some parathyroid gland tissue implanted subcutaneously (Figures 5 and 6). The implanted parathyroid tissue would continue to secret PTH to maintain normal serum calcium. The usual site of implantation was the forearm but our team also implanted the tissue in the thigh, so as to avoid interference with AV fistula creation, should that be needed in the future (Figure 7). Alternatively, one can leave some parathyroid tissue in-situ during the parathyroidectomy ('removing three and a half glands'). After the operation, the serum PTH falls rapidly and great improvements in the radiological changes follow (Figures 8 to 10).

Advances after the 1990's

Considerable progress was made in the field of renal SHPT in the 1990's with important clinical significance.

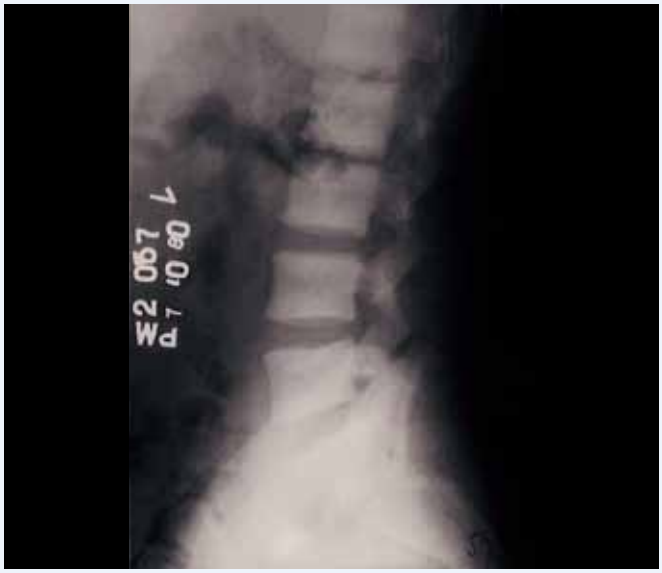


Figure 3. SHPT: The rugger jersey spine.

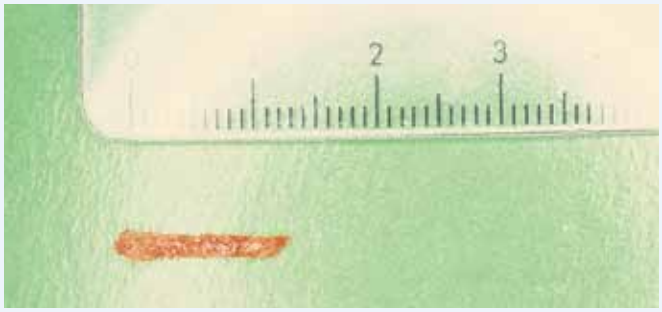
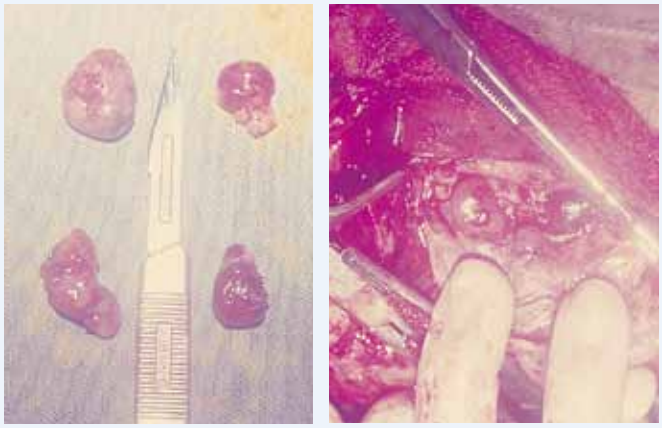


Figure 4. A bone biopsy specimen.



Figures 5 and 6. Parathyroidectomy for SHPT.

Stratification of renal failure patients

Chronic renal failure patients are said to be suffering from CKD. It was found that patients with different degrees of renal impairment could be stratified according to the remaining renal function, usually by the estimated glomerular filtration rate (eGFR). It was calculated from the MDRD equation using the serum creatinine and other parameters depending on the age, sex and race of the patient. It was divided into five stages according to the residual renal function. The full details are described elsewhere [1]. Apart from specific measures to treat the primary causes, the management of CKD patients in the same stage is similar irrespective of the primary pathology.

Relationship between SHPT and cardiac mortality in renal patients.

The development of chronic dialysis is a milestone in nephrology [2]. After decades of 'success', nephrologists looked at the survival data and they were surprised to find that a high percentage of renal patients died of cardiovascular disease. In the United States, the annual mortality of the dialysis patients was around 20%. Such increased risk could not be solely explained by the usual risk factors such as hypertension, diabetes mellitus and hyperlipidaemia. The increase in cardiovascular mortality is due to the presence of vascular calcification, both in the intima and the media of the blood vessels (Figure 11). In contrast, the vascular calcification of atherosclerotic patients is mainly confined to the intima. This prompted workers to look at SPHT and the calcium metabolism as causative factors of vascular calcification and heart attacks.

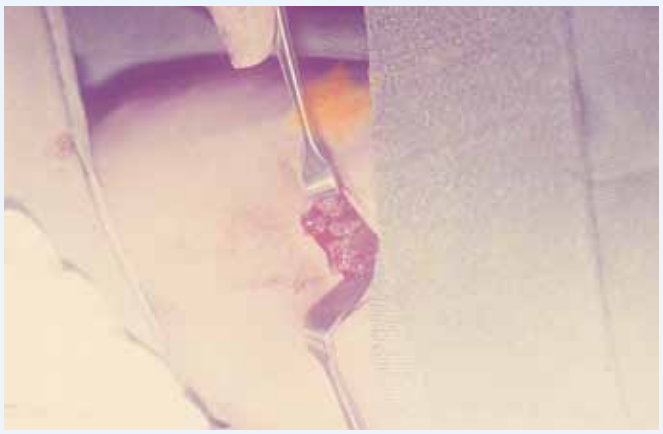


Figure 7. Implantation of some parathyroid tissue in the thigh.

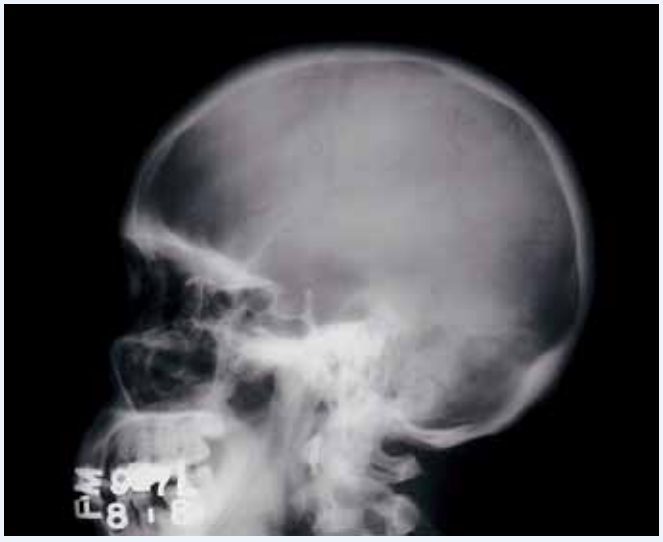


Figure 8. The skull X-ray of the same patient after parathyroidectomy.

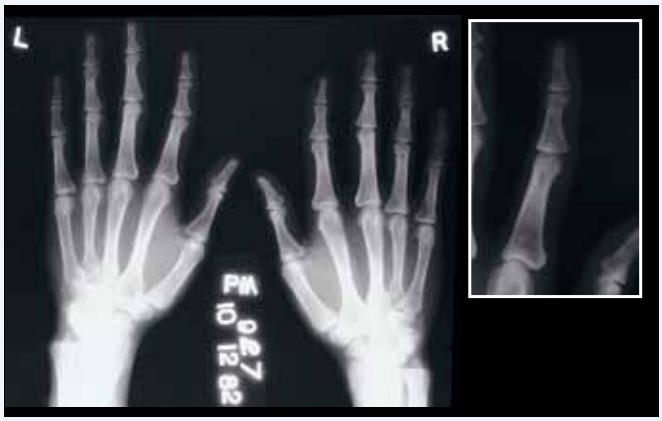


Figure 9. X-ray of the hands of the same patient after parathyroidectomy.

1. Hypercalcaemia
   It is well known that high blood calcium accelerates vascular calcification. Hypercalcaemia in CKD patients is usually caused by calcium-based phosphate binder

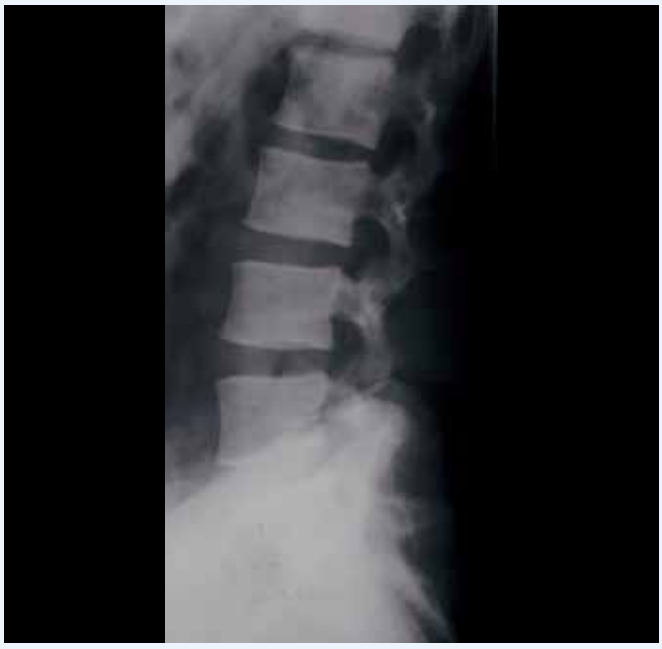


Figure 10. Spine X-ray of the same patient after parathyroidectomy.

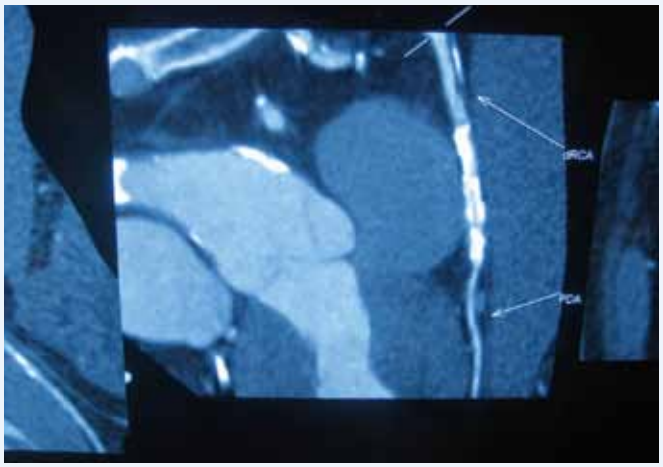


Figure 11. Coronary vascular calcification in a CKD stage 5 patient.

administration (calcium carbonate or calcium acetate) or calcitriol overdosage.

2. Hyperphosphataemia.
   Serum phosphate levels start to rise in CKD stage 3 when the GFR is reduced to 40 mL/minute. It was postulated that normal phosphate levels were maintained in early CKD because the high PTH levels caused increased urinary phosphate excretion. High phosphate would also accelerate vascular calcification. It was found that an increase of 1 mg/dL of serum phosphate would cause a 6–8% increase in cardiovascular mortality.

3. Hyperparathyroidism (SHPT)
   SHPT occurs early in CKD. PTH levels are significantly increased in CKD stage 2–3. SHPT is an important risk factor for cardiac mortality. PTH causes hypercalcaemia, and increases the transformation of the vascular smooth muscle cells to osteoblast-like cells, predisposing vascular calcification. This causes increased arterial stiffness and increases the after load of the heart. It has been shown that treatment of SHPT causes improvement in cardiovascular mortality.

The patho-physiology of SHPT

1. The control of PTH secretion was better understood. Hypocalcaemia is known to be a potent stimulus for PTH secretion as part of the biofeedback loop maintaining normal calcium levels. It was found that there were calcium receptors in the chief cells of the parathyroid glands. Low calcium levels cause low calcium receptor activation with increased secretion of PTH. The intracellular signal later causes increased production of PTH. Conversely, high calcium combines with the calcium receptors to suppress PTH secretion.
2. In addition to the calcium receptors, there is another group of receptors in the chief cells called vitamin D receptors (VDR). When vitamin D combines with the receptor, there will be signal transduction causing the suppression of PTH secretion. Thus, calcitriol controls SHPT by increasing the serum calcium (by enhancing calcium absorption in the gut) and also direct suppression through its action on the VDR.
3. Apart from calcitriol, there are other vitamin analogues which can also bind to VDR. They are collectively known as vitamin receptor activators (VDRA). Such drugs include doxercalciferol (1-alpha-hydroxyvitamin D2) and paricalcitol (Zemplar®); their molecular structures are shown in Table 1. It can be seen that they are very similar molecules. These new VDRA have a greater ability to suppress PTH secretion and with less tendency to cause hypercalcaemia.
4. PTH is a polypeptide hormone with 84 amino acids. In CKD patients, PTH fragments from metabolic breakdown accumulate in the blood stream. Such fragments may not have biological activities but would still be detectable by essays detecting the N-terminal or C-terminal of PTH. Thus detection of iPTH is the assay of choice in renal failure patients. New radioimmunoassays aimed at detecting PTH (1–84) fragments have been developed. The whole PTH immunoradiometric assay—a third-generation assay—uses a detection antibody that recognizes antigenic determinants at the extreme amino-terminal (1–4) end of the PTH molecule, making the assay specific for biologically active whole PTH-(1–84).

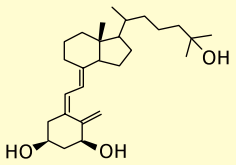
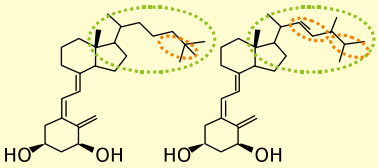
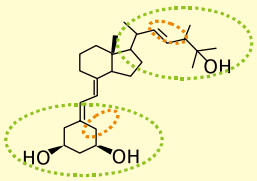
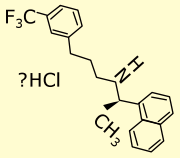
Clinical implications

The new understanding in SPHT has an important bearing on its clinical management. In addition to causing bone changes, SPHT will enhance vascular calcification with increased cardiovascular mortality. Thus the management of SPHT has an important effect on patient survival.

Since SPHT develops early in CKD stage 2 in which the GFR is around 60–89 mL/minute, treatment has to be started early. iPTH should be measured in early CKD patients and active vitamin D preparations should be given if there is evidence of SHPT. As the disease progresses, phosphate retention will set in and the administration of a phosphate binder in addition to dietary phosphate restriction would be needed. The phosphate binders are usually calcium based, such as calcium carbonate or calcium acetate. Aluminum hydroxide or magnesium hydroxide can also be used, but there are worries about aluminum absorption and accumulation in renal patients.

Recently, a resin known as simvelar (Renagel®) has been made available. It is an effective non-calcium based phosphate binder which does not cause hypercalcaemia.

Table 1. Vitamin D receptor analogues.

Non-Selective VDRA		Selective VDRA	Calcimimetics
1st Generation	2nd Generation		
			
Calcitriol 1α,25-dihydroxyvitamin D_3	**Alfacalcidol/Doxercalciferol** 1α-hydroxyvitamin D_3/D_2	**Paricalcitol** 19-nor-1α,25-dihydroxyvitamin D_2	**Cinacalcet**
Mimics endogenous VDR hormone	Molecular modifications at the side-chain	Molecular modifications at the side-chain and A-ring	CaR activator
Calcijex® (IV) Rocaltrol (Oral) Generics (IV & Oral)	One Alpha Hectorol®	Zemplar®	Sensipar® Mimpara®
SHPT in CKD (pre-analysis) Osteoporosis, Hypocalcemia	SHPT in CKD Osteoporosis, Hypocalcemia	SHPT in CKD (Stage 3, 4, 5)	SHPT in CKD (Stage 5 only)

The main drawback is the expense and the number of tablets needing to be taken. A new compound, lanthanum carbonate, has recently been available as an effective phosphate binder, and again the cost is the main concern.

Vitamin D analogues are the mainstay of SPHT treatment. They act by increasing the serum calcium levels through gut absorption and hence suppresses PTH secretion by the calcium receptor activation in the parathyroid gland. The vitamin D analogues also down-regulate PTH secretion through the vitamin D receptors. Calcitriol was the first to be used. It was effective but the limiting factor is hypercalcaemia. The 'third generation vitamin D', paricalcitol, is now receiving increasing attention. It is effective in lowering PTH levels without much risk of hypercalcaemia. It can be given orally in early renal failure patients and in patients undergoing haemodialysis, it can be given intravenously as a 5 μg dose after each dialysis. The dose needs to be titrated according to the serum calcium and PTH levels. The drug was shown to effective in the reduction of cardiovascular mortality.

Apart from the vitamin D analogues, there is a new group of drugs called 'calcimimetics'. They suppress secretion of PTH by increasing the sensitivity of the calcium receptors to serum calcium. The action of this class of drugs is dependent upon calcium-induced spatial modification of its calcium-sensing receptor and not actually mimicking the calcium ion but popular usage has established their name as 'calcimimetics'. Cinacalcet (Sensipar®) is the first-in-class calcimimetic agent approved for treatment of SHPT. It is useful in resistant SHPT and is available in Hong Kong on a 'named patient' basis. Again cost is a great concern.

The interpretation of the PTH can be complicated. Firstly the units used in America and Europe are different. The former uses metric units (pg/mL) while the latter uses SI units (pmol/L). Secondly the 'target' PTH level is different in different stages of CKD (see Table 2 for easy reference). In Hong Kong, different labs use different units, and most laboratories only give the reference value for patients with normal renal function. We recommend that the laboratories give the target values for different stages of CKD as well.

Management of calcium metabolism and SHPT in CKD patients requires a lot of effort from the renal team with meticulous attention to the calcium, phosphate and iPTH levels (Table 3). It is rewarding because it has significant positive impact on the outcome. The best results can only

Table 2. Recommended PTH levels in CKD.

CKD stage	e-GFR (mL/min/1.73 m^2)	iPTH (pmol/L)	iPTH (pg/mL)
3	30–59	3.5–7.4	35–70
4	15–29	7.4–11	70–110
5	<15	16–33	150–300

National Kidney Foundation. K/DOQI Clinical Practice Guidelines for Bone Metabolism and Diseases in CKD 2003.

Table 3. Recommended guidelines for patients with CKD stage 5.

	KDOQI (2003)	CARI (2006)	EBRG (2002)
Calcium	2.1–2.4	2.1–2.4	2.2–207
Phosphate	1.1–1.8	0.8–1.6	0.8–1.5
Ca x P	<4.3	<4.0	
iPTH	16.5–33	2–3 x ULN	9–18

K/DOQI: Kidney Disease Outcomes Quality Initiative; CARI: Caring for Australians with renal impairment; EBPG: European Best Practice Guidelines; ULN: upper limits of normal

achieved by teamwork, involving the renal physician, the renal nurses and the dietitian. A clinical audit would be a useful tool for the outcome assessment.

Conclusion

SHPT develops early in renal failure. Apart from its effect on the bones, it is now known that SHPT is a significant risk factor for vascular calcification and cardiac mortality. This causes a paradigm shift from the bone to the 'bone and blood vessels'. Early treatment is essential for prevention of cardiac mortality. With the development of new VDRAs, we are now able to deliver better treatment since the discoveries of Hector DeLuca 30 years ago.

References

1. Ho CP. Chronic kidney disease (CKD) – Old diseases with new global challenges. *HKMA CME Bulletin* April 2008, p 4–7.
2. Ho CP, Au YF. Haemodialysis – what have we learnt in the past three decades? *HKMA CME Bulletin* June 2008, p 4–9.

Q&A

Answer these on page 16 or make an online submission at: www.hkmacme.org

Please indicate whether the following questions are true or false

1. The increased PTH secretion causes hypercalcaemia with clinical manifestations of bone resorption, urinary stones and abdominal pain.
2. In the early 1980's, Hector DeLuca made the landmark discovery that the native vitamin D (cholecalciferol) has to be converted in the liver to 25 hydroxy-vitamin D and then to 1,25 dihydroxy-vitamin D3 (calcitriol), the active hormone, in the kidneys.
3. The commonest pathology caused by SHPT is osteitis fibrosa cystica with bone resorption.
4. There were no drawbacks of calcitriol administration.
5. If the SHPT could not be adequately controlled despite medical therapy, surgical hyperparathyroidectomy was performed.
6. Apart from specific measures to treat the primary causes, the management of CKD patients in the same stage is similar irrespective of the primary pathology.
7. In the United States, the annual mortality of the dialysis patients was around 40%.
8. It was found that an increase of 1 mg/dL of serum phosphate would cause a 6–8% increase in cardiovascular mortality.
9. Detection of iPTH is the assay of choice in renal failure patients.
10. Europe uses metric units (pg/mL) while America uses SI units (pmol/L) in interpretation of PTH levels.

ANSWERS TO FEBRUARY 2009

Family doctors can help young drug abusers

1. True	2. False	3. True	4. True	5. False
6. True	7. True	8. True	9. True	10. True