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Epidemiology and Prevention

Chronic kidney disease and secondary hyperparathyroidism in children

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Introduction

Chronic kidney disease (CKD), a significant health problem with many adverse complications, affects approximately 14.5% of US population (1). In the past two decades the incidence of renal failure is not only rising among adults but also in children (2). CKD is defined as "evidence of structural or functional kidney abnormalities (abnormal urinalysis, imaging studies or histology), that persists for at least three months, with or without a decreased glomerular filtration rate (GFR), as defined by a GFR of less than 60 ml/min per 1.73 m^2, by KDIGO (2). Some adverse effects of CKD may act as progressive factors to end-stage renal failure (ESRD). Among these factors, osteodystrophy, systemic and intraglomerular hypertension, glomerular hypertrophy, proteinuria, tubulointerstitial disease are remarkable (2). Secondary hyperparathyroidism is a well-known independent risk factor of developing bone disease, vascular calcification, and all-cause mortality and morbidity even in non-CKD patients (3-6). Although most guidelines recommend prescription of vitamin D analogs in pre-dialysis CKD patients, there is no consensus on dose, time of prescription, type of analog (D2 or D3) and duration of prescription of vitamin D.

Implication for health policy/practice/research/medical education

Secondary hyperparathyroidism is a well-known independent risk factor of developing bone disease, vascular calcification, and all-cause mortality and morbidity even in end-stage renal disease (ESRD) patients and patients under hemodialysis.

Vitamin D analogs, preparations, prescription, doses and intervals

Keeping optimal bone turn-over needs using vitamin D analog from early stages of CKD (stage 3) (1). KDOQI and kidney disease improving global outcomes (KDIGO) recommend either D2 or D3 analog interchangeably in pre-dialysis stages (7). Vitamin D derivatives (vitamin D receptor activators; VDRAs) are divided into two groups (8):

a) Non- selective and agonist activators (VDRAs)

b) Selective VDRAs

Non-selective VDRAs are most popular and include; calcitriol (1α,25(OH)2D3), alfacalcidol(1α,25(OH)D3) and doxercalciferol(1α,25OHD2).

Most studies on administrating non-selective VDRAs and ergocalciferol support the effectiveness of these compounds on secondary hyperparathyroidism (SHPT) in early stages of CKD (9-14). Regarding the results of most studies, administrating VDRAs in CKD stage 3-4 with parathormone (PTH) more than 70-100 ρg/ml, blood calcium less than 9.5 mg/dl and phosphorus less than 4.6 mg/dl is recommended (7). However, in advanced stages of CKD, administration of alfacalcidol showed the most promising results (15).

Vitamin D analog may result in hypercalcemia even in low doses (16). Therefore, monthly monitoring of serum calcium and phosphorus at first and then every three months is recommended. Intact serum PTH level should be checked every 3-6 months (1).

Selective VDRAs (paricalcitol, maxacalcitol, falecalcitriol) are analogs of vitamin D that have been developed not only to inhibit PTH secretion but also to decrease activation of vitamin D receptor elsewhere (17). With an extended inhibitory effect of paricalcitol on PTH secretion, this medication suppresses pre-pro- PTH mRNA synthesis (18). Hypercalcemia and hyperphosphatemia are less prevalent with selective VDRAs than non-selective VDRAs. In addition, lower amount of calcium-phosphorus product has been reported with paricalcitol (19).

However, in a recent meta-analysis on 76 trials, Palmer *et al.* (20) showed that vitamin D compounds did not reduce the risk for death, bone pain, vascular calcification, or parathyroidectomy. In addition, this meta-analysis revealed that vitamin D prescription did not reduce PTH levels consistently.

Considering the frequency of treatment, CARI guideline (caring for Australians with renal impairment; also known as CARI guidelines) suggested daily oral intake (total) of vitamin D for patients with early chronic kidney who are not exposed to direct sunlight for at least 1-2 hours per week as follows (21):

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19-50 years: 5 µg (200 IU)
51-70 years: 10 µg (400 IU)
>70 years: 15 µg (600 IU)
Single monthly 50,000 IU ergocalciferol capsule was effective in reversing vitamin D level to normal values within six months (22).
Panichi *et al.* (12) reported more effectiveness of thrice–weekly oral administration of calcitriol than daily and or once a week prescription on PTH level.
Selective VDRAs have been used recently with encouraging results. Intravenous administration of paricalcitol (Zemplar®) as a dose of 5 µg after each dialysis was effective in controlling SHPT and preventing hypercalcemia. Some studies on adult patients with CKD stage 3-4 showed that oral capsules of paricalcitol (1 µg daily or 2 µg thrice weekly) could decrease PTH efficiently (23,24).

Phosphorus chelating agents

Hyperphosphatemia is an important risk factor of cardiovascular and bone diseases in CKD patients (25-27). PTH synthesis and secretion that are induced by hyperphosphatemia prime glandular hyperplasia of parathyroid gland (28). In addition, hyperphosphatemia accelerates kidney failure progression. The vicious cycle between hyperphosphatemia and kidney failure leads to poor metabolic control of calcium and phosphate (29). Regarding the crucial role of phosphate in increasing risk of mortality and morbidity of CKD patients, decreasing its level is mandatory. Although, administration of vitamin D analogs decreases PTH secretion these products aggravates intestinal phosphate absorption. Therefore, phosphorus chelating agents have been introduced to CKD medication regimens. A various kinds of phosphate chelating agents are now available. Among these medications, aluminum hydroxide is one of the most potent drugs. Nevertheless, serious side effects including osteomalacia, myopathy, loss of appetite, constipation, microcytic anemia and encephalopathy limit its widespread usage (30,31). Calcium-containing phosphate binders include calcium carbonate (CaCO3, elemental calcium content 40%) or calcium acetate (CaAc, elemental calcium content 25%) are two medications that are used widely. Two more phosphate chelating agents include sevelamer HCl, and lanthanum carbonate. However, the European pediatric dialysis working group (EPDWG) recommends not only restricting phosphate intake but also using calcium – containing phosphate binders as the first line of CKD regimens when hyperphosphatemia occurs (GFR less than 40 ml/min/1.73 m^2) (32,33). Furthermore, by regular controlling of phosphate, calcium and PTH, the product of calcium-phosphate must be kept below 60 mg^2/dl^2 (32). Less effectiveness of sevelamer HCl in acidic environments limits its usage. Lanthanum carbonate has good efficacy in different PH ranges. Nonetheless, a systematic review by Stuart *et al.* (34) showed effectiveness of all types of phosphate binders in controlling hyperphosphatemia without any priority. Even so, inducing hypercalcemia by calcium based phosphate binders may raise inclination for using sevelamer HCl or lanthanum carbonate instead of calcium- based phosphate binders.

Calcimimetics

This group of drugs act specifically on class C G-protein coupled receptors (calcium sensing receptors; CaSR) on parathyroid gland. High plasma calcium or phosphate in the presence of elevated PTH may be an indication of prescribing calcimimetics (32). While sustain decreasing of PTH occurs by using these medications, no increasing calcium-phosphorus product has been reported in CKD patients (35,36). A recent study on rats supported the preventive and reversing effects of cinacalcet on glandular hyperplasia of parathyroid gland (37). There are limited studies on using calcimimetics in pediatric CKD patients. However, encouraging results from adult studies are approaching. In CKD stage 3-5, the reducing effect of cinacalcet on serum PTH has been shown (38). A meta-analysis by Palmer *et al.* (39) showed that cinacalcet decreased the need for parathyroidectomy in CKD stage 5 but had no effect on all-cause mortality. Schlieper *et al.* (40) reported safety of calcimimetic (cinacalcet) in CKD children stages 3-4. However, limited studies on children precludes wide spread usage of this group of medications in children. Side effects of cinacalcet include nausea, vomiting and transient hypocalcemia are not very common and in most cases did not result in discontinuing treatment (41).

Parathyroidectomy

EPDWG recommends parathyroidectomy in the event of severe hyperparathyroidism (PTH > 800 ρg/ml) with radiological signs in combination with hypercalcemia and/or elevated calcium phosphorus product (32). Messa *et al.* (42) implied that severe and uncontrolled SPTH by medical therapy (serum PTH ≥ 600 ρg/ml and serum calcium ≥ 10 mg/dl) is a strong indication of parathyroidectomy. Parathyroidectomy with auto-transplantation of parathyroid followed by kidney transplantation result in good control of calcium- phosphorus product and SHPT in children with CKD stage 5 (43).

Authors' contribution

AG is the single author of the paper.

Ethical considerations

Ethical issues (including plagiarism, misconduct, data fabrication, falsification, double publication or submission, redundancy) have been completely observed by the author.

Conflicts of Interest

There were no points of conflicts.

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