CHAPTER II

REVIEW OF THE RELATED LITERATURES

Before the study began , all the related literatures were reviewed to form the theoretical framework of the study. The literatures were reviewed in topics.:

1) Renal osteodystrophy in chronic renal failure

2) Hyperparathyroidism in chronic renal failure

3) Vitamin D and hyperparathyroid bone disease

4) Prophylaxis treatment of vitamin D in chronic dialysis

Renal osteodystrophy in chronic renal failure

Renal osteodystrophy is the major problem in chronic renal failure patients with long term dialysis. There are three types of osteodystrophy (Andress, and Sherrard, 1993).

a) High turnover bone disease (Hyperparathyroid bone disease)

This type is mediated by a steady state of high levels of parathyroid hormone (PTH). 'The disease will progress from mild disease to severe form called osteitis fibrosa. The typical x-ray features are subperiosteal resorption and osteosclerosis but soft tissue calcification can be seen . The earliest bone histologic change is the increasing of the unmineralized osteoid .In addition ,bone formation rate is either normal or increased . If serum levels of PTH continue to

increase , the more severe form : "osteitis fibrosa" will be observed. Osteoclast will increase in size and number and endosteal fibrosis will become prominent (Andress, and Sherrard, 1993).

b).Low turnover bone disease (Osteomalacia and aplastic bone)

This type is correlated with aluminum accumulation (aluminum-related osteomalacia) ,iron accumulation , low phosphate levels and vitamin D deficiency. Serum parathyroid levels are low . The typical x-ray features are pseudofracture but osteopenia or tissue calcification may be seen . Subperiosteal resorption , the pathognomonic sign of hyperparathyroid bone disease may be frequently seen in patients with osteomalacia. Bone histology of osteomalacia is characterized by an increasing of osteoid . In aplastic bone disease ,there is an additional evidence of decrease bone formation determined by tetracycline uptake (Coburn, and Slatopolsky, 1991).

To exclude aluminum toxicity, random serum aluminum will be evaluated. Serum values below 50 ug per liter essentially exclude aluminum toxicity while values above 300 ug per liter confirm the diagnosis. In cases of serum values between 50 and 300 ug per liter the deferoxamine challenge test will be done. The levels more than 350 ug per liter confirms the presence of biologically significant aluminum accumulation (Andress, and Sherrard, 1993).

c). Mixed osteodystrophy

The histology in this type shows increasing in both fibrosis and osteoid bone as in high and low turnover bone disease. Serum parathyroid levels are high in this type (Coburn, and Slatopolsky, 1991).

In chronic renal failure, secondary hyperparathyroidism was reported as the most common cause of renal osteodystrophy (Sherrard et al , 1974; Smith et al., 1986). The lesion begins in a mild form and progresses to typical osteitis fibrosa (hyperparathyroid bone disease) and is mediated by a steady rising in serum parathyroid hormone (secondary hyperparathyroidism).

CAUSE OF HYPERPARATHYROIDISM IN CHRONIC RENAL FAILURE

The genesis of hyperparathyroidism in renal failure is complex and involves several mechanisms . The first mechanism is hypocalcemia , a major factor leading to secondary hyperparathyroidism in end-state renal disease. Hypocalcemia can arise from :

1).marked hyperphosphatemia . When renal disease advances and glomerular filtration rate (GFR) falls below 25 ml/min ,hyperphosphatemia is common (Goldman, and Bassett, 1954). Under such circumstance hypocalcemia is directly related to the levels of serum phosphate.

2). impaired intestinal calcium absorption due to calcitriol deficiency (Holick, 1987).

3). skeletal resistance to the calcemic action of PTH on bone (Massary et al., 1973).

The second cause of hyperparathyroidism is altered sensitivity of the parathyroid cell to extracellular calcium concentration, with a shift in the "set point" so the higher calcium levels are needed to reduce PTH secretion (Brown et al., 1982). The third mechanism is presenting of calcitriol receptors that suppress the secretion of hormone. Inappropriately low levels of calcitriol may be responsible for continue

PTH synthesis and secretion despite normal calcium levels . This mechanism can cause increasing PTH secretion in the absence of true hypocalcemia. Decreasing of calcitriol in chronic renal failure is one of the important cause of hyperparathyroidism (Delmez, 1989 : Dunlay, 1989).

Calcitriol and other active forms of vitamin D can increase absorption of calcium from GI tract and increase tubular absorption of calcium in the kidneys, these combined actions lead to increasing level of serum calcium.

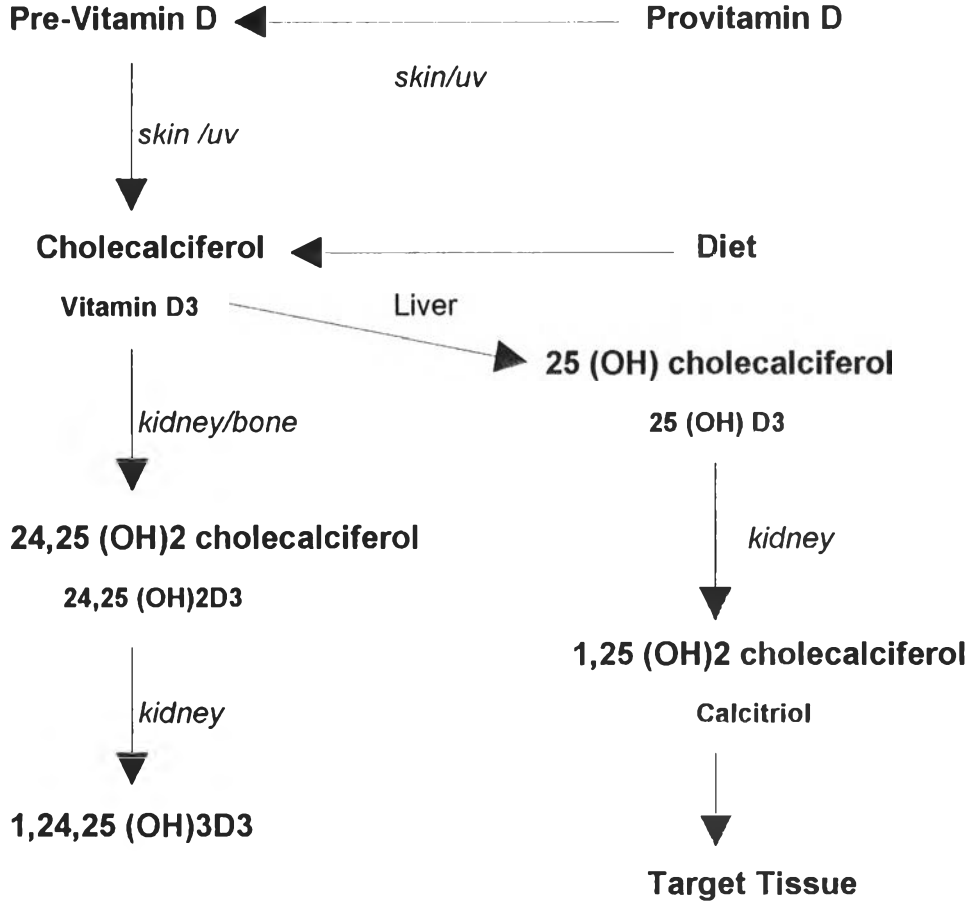
In adults with chronic renal insufficiency (GFR below 40-50 ml/min) the blood levels of calcitriol will be lower than control (Christiansen et al., 1981). Inadequate production of calcitriol reduces intestinal absorption of calcium. This will contribute to the reduction of ionized calcium in the blood thereby stimulating the secretion of PTH and leading to secondary hyperparathyroidism (Slatopolsky et al., 1990).

VITAMIN D AND HYPERPARATHYROID BONE DISEASE

Vitamin D stimulates the intestinal transport of calcium and phosphate and has some direct effect on bone that make the collagen matrix susceptible to normal calcification . Vitamin D deficiency in human can cause osteomalacia , the bone disease which it's mineralization is delayed leading to the fracture of bone (Krane, and Holick, 1994).

Fig 1. Schemetic illustration on the bioactivation of Vitamin D

(Coburn , 1991)



Human can receive vitamin D either from the diet or through ultraviolet irradiation of the compound of provitamin D in the skin. Figure 1. shows the schematic illustration of the bioactivation of vitamin D that may arise from the diet or the skin.

Vitamin D3, 25-(OH) D3 and 1,25 (OH)2D3 are each transported in plasma by binding to the same vitamin D-binding protein. 1,25 (OH)2D3 (1,25 dihydroxy cholecalciferol or calcitriol) is the most potent form of active vitamin D.

Since calcitriol is produced in the kidney , the blood levels of calcitriol will be lower than normal in chronic renal insufficiency. Inadequate levels of calcitriol will reduce intestinal absorption of calcium and lead to reduce levels of blood ionized calcium . This will stimulate the secretion of PTH that cause secondary hyperparathyroidism.

Parathyroid cells were found to have receptors for calcitriol (Korkor, 1987). Calcitriol suppresses the parathyroid cell through several different mechanism: it increases calcium sensitivity (Delmez et al., 1989) : it reduces mRNA for pre-pro-PTH by reducing transcription (Silver et al., 1986) and it inhibits parathyroid cells proliferation (Szabo et al.,1989).

In the other hand, if kidney is the single source of calcitriol production,the supplementation of vitamin D in kidney disease should be only in the form of calcitriol . In contrast, the study performed in dialysis patients, including those who were anephric, was found that the levels of calcitriol were increased after the administration of pharmacological doses of 25-(OH)D3 (Dusso et al. , 1988).

Rudniki et al. (1991), reported the lack of relationship between parathyroid hormone and calcitriol in chronic renal failure. These evidence showed that calcitriol can be produced from extrarenal sources .

The role of 24,25-(OH2)D3 in pathogenesis of renal osteodystrophy remains uncertain. It has been found that this sterol can be produced in the intestine and bone as well. Data on blood levels of this sterol in uremic patients indicating low concentration has been demonstrated. Some observations showed that 24,25 (OH2)D3 was not effective in the treatment of secondary hyperparathyroidism and osteitis fibrosa in animals with experimental renal failure (Olgard et al., 1984). However the role of 24,25-(OH2)D3 in suppression serum parathyroid levels in end stage renal failure has been reported (Ben-Ezer et al., 1991; Varghese, Moorhead and Farrington, 1992).

PROPHYLAXIS TREATMENT OF VITAMIN D IN CHRONIC DIALYSIS PATIENTS

In cases of overt secondary hyperparathyroidism (bone erosis, high PTH level, increase alkaline phosphatase) with adequate treatment by vitamin D often lead to improvement in both continuous ambulatory peritoneal dialysis (CAPD) and hemodialysis patients (Andress et al., 1989).

Prophylaxis use of vitamin D (calcitriol) in hemodialysis patients was proved to effectively suppress parathyroid hormone (Berl et al., 1978; Delmez et al.,1989 ; Gallienti et al., 1992). In the previous studies of calcitriol, it was difficult to determine whether PTH levels were decreased due to a direct inhibitory effect of calcitriol or a calcitriol-induced increasing in the serum calcium. Now it was clear

that the suppressive effect of calcitriol was attained by a direct action on the parathyroid gland rather than by its ability to elevate serum calcium levels (Quarles et al.,1988; Dunlay et al., 1989; Tsukamoto et al. , 1991).

Prophylaxis use of vitamin D in CAPD patients was believed to be benefit as in hemodialysis patients but indeed, there are several differences between CAPD and hemodialysis which can effect renal osteodystrophy . In conclusion the differences between CAPD and hemodialysis which can effect osteodystrophy are:

1). increasing losses of serum albumin and other peptides in peritoneal dialysate, compared to little or no loss during hemodialysis. Lower serum albumin levels in CAPD patients lead to less binding of calcium in serum . The ionized calcium is thus higher and PTH levels often lower (Salusky et al.,1987).

2) The net removal of phosphate may be slightly higher in CAPD than in hemodialysis (Cannata et al., 1983).

3) There is flux of PTH and its fragments into the peritoneal dialysate. The peritoneal clearance of C-terminal PTH is correlated closely with inulin clearance (Delmez et al., 1982).

4) there is the loss of the vitamin D-binding protein , a microglobulin with molecular weight of 57000 daltons , along with 25- hydroxy-vitamin D and calcitriol in CAPD (Guillot et al., 1983).

The bioalailability of calcitriol was evaluated after single oral, intravenous,and intraperitoneal doses of 60 ng/Kg in CAPD patients. The serum levels of calcitriol were found similar in all routes at 24 hours

(Salusky et al.,1990). This study showed that oral form of vitamin D should be appropriate to give to the patients.

In CAPD patients some investigators have reported that dietary restriction of phosphates and oral calcium supplementation provides good control over the evolution of renal osteodystrophy, suggesting that the administration of vintamin D metabolites could be avoided (Coburn, 1980 : Delmez, et al.,1986.: Shusterman, et al., 1985). In contrast, previous studies reported an increasing of renal osteodystrophy and secondary hyperparathyroidism (Atkinson et al., 1973; Parfitt et al., 1976: Buccianti, Bianchi, and Valenti ,1984). In children , treatment with vitamin D in CAPD cases was proved to be benefit in regression of bone disease and increasing the patients growth rate (Watson et al. 1988). In adult , Buccianti (1990) , used calcifediol in all cases of CAPD and found the benefit in renal osteodystrophy. Prophylaxis treatment of vitamin D still lacks of double blind controlled trial to prove the benefit in adult patients on CAPD.

Summary

In chapter II , an overview of the renal osteodystrophy and hyperparathyroidism in chronic renal failure, vitamin D and hyperparathyroid bone disease as well as prophylaxis treatment of vitamin D in chronic dialysis have been reviewed and presented.