CHAPTER II
LITERATURE REVIEW

This chapter is description of the significance of mineral and bone disorder in patient with CKD and the studies of adherence to K/DOQI clinical practice guideline for bone metabolism and disease 2003 in CKD patients.

2.1 Significance of mineral and bone disorder in patient with CKD

2.1.1 The study of association between mineral metabolism disorder and the mortality risk in the patient with CKD

A study was indicated that the patients with CKD stage 3 and 4 had normal range of serum phosphate until GFR was lower than 40 ml/min/1.73 m^2. From this point, level of phosphate will increase sharply because of decreasing of GFR. Increasing in each 1 mg/dl of serum phosphate was increasing in mortality risk and acute myocardial infraction about 23% and 35%, respectively. Also the study was found that serum phosphate higher than 3.5 mg/dl would increase the risk of death to 32%, comparing with 2.5-2.9 mg/dl of phosphate level. (Kestenbaun et al., 2005)

Mortality risk in hemodialysis patients was 17.5% in mineral and bone disorder which was more than any other mortality risk, 11.3% for anemia and 5.1% for inefficient dialysis. Phosphate level which was lower than 3.0 mg/dl or higher than 5.5-6.0 mg/dl when compared with phosphate level of 4.0-5.0 mg/dl increased mortality risk to 10% and 25%, respectively. The serum level of albumin-adjusted calcium higher than 9.5-10 mg/dl increased mortality risk approximately 17% when compared with serum albumin-adjusted calcium 9.0-9.5 mg/dl. Calculated serum CaxP product more than 45-50 mg^2/dl^2 increased mortality risk 15% when compared with serum calculated CaxP product 40-45 mg^2/dl^2. Serum PTH higher than 600 pg/ml increased mortality risk to 20%, comparing with serum PTH 150-300 pg/ml. (Block et al., 2004)

The data in patient with CKD stage 5 who had on hemodialysis for more than 1 year, phosphate level of 6.5 mg/dl were poor controlled. Serum phosphate

higher than 6.5 mg/dl increased risk of death 27% when compare with serum phosphate 2.4-6.5 mg/dl. CaxP product higher than 72 mg^2/dl^2 increased mortality to 15% when compared with CaxP product 42-52 mg^2/dl^2. (Block et al., 1998)

The phosphate level which was higher than 5.5 mg/dl significantly increased mortality risk 40% in hemodialysis patients and 60% in continuous ambulatory peritoneal dialysis patients when compare with phosphate level of 3.5-5.5 mg/dl. Additionally, CaxP product that higher than 55 mg^2/dl^2 had significant increasing risk of death 40% in hemodialysis patients and 50% in continuous ambulatory peritoneal dialysis patients when compare with CaxP product that lower than 55 mg^2/dl^2. (Noordzij et al., 2005)

The study in Japan claimed that the all cause mortality rate in hemodialysis patient increased to 22% when serum calcium enhanced in each 1 mg/dl and to 4% when serum PTH increased in each 100 pg/ml. Moreover mortality rate from cardiovascular cause significantly increased about 28% when rising in each 1 mg/dl of calcium, 13% in each 1 mg/dl of phosphate, 7% in each 5 mg^2/dl^2 of CaxP product and 8% in each 100 pg/ml of PTH, respectively. Serum phosphate higher than 6.5 mg/dl and lower than 3.5 mg/dl enhanced mortality risk to 33% and 61%, subsequently, when compared with serum phosphate 4.5-5.5 mg/dl. Calcium level higher than 10.4 mg/dl increased mortality risk to approximately 53%, and mortality risk from cardiovascular cause increased 2.29 times, when compared with calcium level 8.4-9.0 mg/dl. PTH level higher than 500 pg/ml raised mortality risk from cardiovascular cause about 2.01 times, when compared with PTH level 101-300 pg/ml. (Kimata et al., 2007)

2.2 Adherence to K/DOQI clinical practice guideline for bone metabolism and disease 2003

2.2.1 The study of mortality

The cohort study in the United State reported that controlling of calcium, phosphate and PTH value according to K/DOQI targets associated with mortality rate in hemodialysis patients. The data from 2,937 of hemodialysis patients was found that controlling of clinical parameters for mineral and bone disorder within target recommendation were strong evidence to predict survival in hemodialysis

patients. The evidence was indicated that the patient whom all of three clinical parameters could not be controlled had significant increased in mortality risk to about 51% when compared with the controlled patient. Moreover the patient who achieved any target of any one of three clinical parameters or maintained target for any two of three clinical parameters had significant increased approximately 35-39% and 15-21% risk of death, respectively, when compared with those who achieved all of three clinical parameters. Also the patients who maintained calcium, phosphate and PTH value according to guideline targets for 4 quarters had significant decreased mortality risk about 14%, 38% and 25%, respectively when compared with those who achieved less than 1 quarter. (Danese et al., 2008)

2.2.2 The study of clinical parameters measurement.

Retrospective cohort study in 793 patients diagnosed with 424 for CKD stage 3, 212 for CKD stage 4 and 157 for CKD stage 5 described frequency of clinical parameters testing according to K/DOQI clinical practice guidelines for bone metabolism and disease. The results were stated that the patients had done 12.1%-90.8% monitoring for calcium, 5.7%-26.7% for phosphate and 0.5%-7.3% for PTH respectively. By the way the patient with CKD stage 3, 4 and 5 had been testing approximately 90.8%, 64.2% and 12.1% for calcium, 26.7%, 15.1% and 5.7% for phosphate and 7.3%, 0.5% and 3.2% for PTH respectively. (Hoy et al., 2007)

2.2.3 The study of using of phosphate binders

The retrospective study in 283 hemodialysis patients reported the using of calcium base phosphate binders in 1 month. Calcium based phosphate binder were ordered 172 from 283 hemodialysis (61%) patients. 50 from 172 hemodialysis patients (29%) did not follow K/DOQI clinical practice guideline, calcium based phosphate binder was prescribed more than 1,500 milligrams of calcium in 17 hemodialysis patients and did not stop using calcium based phosphate binder when serum calcium excess 10.2 mg/dl in 8 hemodialysis patients. Concurrent use of vitaminD_3 and calcium based phosphate binder were used in 27 hemodialysis patients. Only 2 from 27 hemodialysis patients, dosage of calcium based phosphate binder were decreased when serum calcium excess 10.2 mg/dl. Similarly 10 from 27 hemodialysis patients, calcium base phosphate binder were not discontinued when two consecutive PTH were lower than 150 pg/ml. (Shastri J. et al., 2008)

2.2.4 The study of achieving K/DOQI target recommendations.

The cross-sectional study in 140 hemodialysis patients was indicated that the total of 840 laboratory determinations for each mineral and bone disorder clinical parameters were within K/DOQI target recommendations as follow; 49% for serum calcium, 36% for serum phosphate, 57% for serum CaxP product and 20% for serum PTH. Only 7% of determinations met all of four clinical parameters target recommendation. The percentage of patients who never achieved K/DOQI target recommendations for serum calcium, phosphate, CaxP product and PTH were 19%, 25%, 14% and 63%, respectively. Furthermore 88% of patients never achieved all of four clinical parameters target recommendation. During 6 months period of the study was found that the percentage of each patient who met K/DOQI target recommendations more than 50% were 39% for serum calcium, 16% for serum phosphate, 40% for serum CaxP product and 1% for serum PTH. None of patients met all of four target recommendation achievement more than 50%. (Al Aly et al., 2004)

The cross-sectional study in Spain included 2,392 hemodialysis patients. Mean age was 65.8 years old. The results were stated that mean of serum calcium were 9.57 ± 0.7 mg/dl, phosphorus 4.97 ± 1.5 mg/dl, PTH 297 ± 353 pg/ml and CaxP product 47.5 ± 15 mg^2/dl^2. The percentage of patient achieved target recommendations according to K/DOQI guidelines 2003 were as follows: 45% for calcium, 55% for phosphorus, 73% for CaxP product and 26% for PTH levels. Finally, only 7.3% of patients achieved all four K/DOQI target recommendations. (Maduell et al., 2005)

The cross-section study was performed in 63 hemodialysis patients and mean age 44.19 years old at Jordan University Hospital (JUH), Amman, Jordan. Bone disorders were diagnosed in 45 patients on x-rays as follow; 43 patients (68.3%) for osteopenia, 24 patients (38.3%) for subperiosteal resorption and 22 patients (35%) for metastatic calcification. The percentage of patient who achieved K/DOQI target recommendations were 63.5% for serum calcium, 50.8% for serum phosphate and 21.3% for serum PTH. (Younes et al., 2006)

The retrospective study in 190 hemodialysis patients who had at least 3 months of hemodialysis and treatment according to K/DOQI clinical practice guideline 2003 the data was indicated that the percentages of patient who were within

K/DOQI target recommendations were 53.7% for serum calcium, 57.1% for serum phosphate, 71.7% for CaxP product and 31.1% for serum PTH. (Rivera et al., 2006)

The cross-sectional study was performed in 600 patients with CKD, they were classified as 36.7% CKD stage 3, 27.5% CKD stage 4 and 6.3% CKD stage 5. Achievement of clinical parameters according to K/DOQI target recommendation were evaluated. The percentages of patient with CKD stage 3, 4 and 5 for serum calcium achievement were 71%, 74% and 71%, respectively. The percentages of patient with CKD stage 3, 4 and 5 for serum phosphate achievement were 89%, 80% and 74%, respectively. The percentages of all patients with CKD stage 3, 4 and 5 for CaxP product achievement were 99.5%. The percentages of patient with CKD stage 3, 4 and 5 for serum PTH achievement were 28.8%, 14.5% and 13%, respectively. (Verdallas et al., 2007)

The cross-sectional study in 1,836 pre-dialysis patients classified as 856 patients with CKD stage 3, 354 patients with CKD stage 4 and 111 patients with CKD stage 5 was to determine the achievements of clinical parameters according to K/DOQI target recommendation. The percentage of patient with CKD stage 3, 4 and 5 achieved K/DOQI target recommendations were as follow; 90.7%, 85.6% and 55% for serum calcium, 90.0%, 77.1% and 70.3% for serum phosphate, 99.9%, 98.6% and 93.8% for CaxP product and 42.4%, 24.5% and 31.5% for serum PTH. Finally, 34.9% 18.4% and 21.6% of patient with CKD stage 3, 4 and 5 were within all of four clinical parameters target recommendation, respectively. Abnormalities of serum PTH and vitaminD_3 were found in early CKD stage. In advanced stage of CKD increasing of phosphate and PTH level but decreasing of calcium level would be found. (Craver et al., 2007)

The cross-sectional study in 1,312 hemodialysis patients was stated that the percentage of patient who met K/DOQI target recommendations were 50% for serum calcium, 54% for serum phosphate, 67% for CaxP product and 23% for serum PTH. (Lorenzo et al., 2008)

The summarization of the studies of K/DOQI target recommendations achievement in patient with CKD was shown in Table 1.

2.3 The study of mineral and bone disorder in Thailand

From cross sectional study in 293 hemodialysis patients who had 41.6 ± 10.8 years mean of age, 9.9 ± 0.8 mg/dL mean of calcium level, 5 ± 1.3 mg/dL mean of phosphate level and 445 ± 558.2 pg/mL mean of PTH level. The study was concluded that there were significant correlation between serum PTH and risk factors such as CaxP product, alkaline phosphatase and duration of hemodialysis. These risk factors were the predictable factor for secondary hyperparathyroidism. (Suwarat T. et al., 2004)

Table 1 The summarization of the studies of K/DOQI target recommendations achievement in patient with CKD

Study	Design (N)	Duration	Classification of CKD (N)	Baseline characteristic					Patient achieve target Recommendations (%)				
				Age rage [Mean (SD)]	Male (%)	Co-morbidity (%)	Phosphate binder (%)	Vitamin D_3 (%)	Ca	P	CaxP	PTH	ALL
Al Aly et al. (2004)	Cros-Sectional (N=140)	> 6 month	HD	62 (8.2)	66	-	treatment	treatment	39[a] 49[b]	16[a] 36[b]	40[a] 57[b]	1[a] 20[b]	0[a] 7[b]
Maduell et al. (2005)	Cros-Sectional (N=2,392)	-	HD	65.8 (14)	62	-	-	-	45	55	73	26	7.3
Younes et al. (2006)	Cros-Sectional (N=63)	6 month	HD	44.19	60.3	-	100	55.5	63.5	50.8	-	21.3	-
Rivera et al. (2006)	Retrospective (N=190)	1 years	HD	70	58.2	-	treatment	treatment	53.7	57.1	71.7	31.1	25.2
Craver et al. (2007)	Cross-sectional (N=1,836)	-	CKD3 (856) CKD4 (354) CKD5 (111)	72 (12) 75 (12) 74 (15)	60.4 69.8 60.4	DM(27.7) DM(28.8) DM(27.0)	2.5 19.8 51.4	0.6 7.9 27	90.7 85.6 55	90.9 77.1 70.3	99.9 98.6 93.8	42.4 24.6 46.9	34.9 18.4 21.6

Table 1 The summarization of the studies of K/DOQI target recommendations achievement in patient with CKD (Cont.)

Study	Design (N)	Duration	Classification of CKD (N)	Baseline characteristic					Patient achieve target Recommendations (%)				
				Age rage [Mean (SD)]	Male (%)	Co-morbidity (%)	Phosphate binder (%)	Vitamin D_3 (%)	Ca	P	CaxP	PTH	ALL
Verdallas et al. (2007)	Cros-Sectional (N=600)	4 month	CKD3 (220) CKD4 (165) CKD5 (38)	62.8 (6.2)	56.5	DM (25.7) HT (64.5)	6	18.7	71 74 71	89 80 74	99.5	28.8 14.5 13	-
Lorenzo et al. (2008)	Cross-sectional (N=1,312)	-	HD	62 (16)	59	DM(23)	71	33	50	54	67	23	-

ALL: calcium, phosphate, calcium x phosphate product and PTH level, Ca: calcium, CaxP: calcium x phosphate product, CKD: chronic kidney disease, DM: diabetes mellitus, HD: hemodialysis, HT: hypertension, M: male, P: phosphate, PTH: parathyroid hormone

[a]; Meet K/DOQI target recommendations >50%

[b]; 840 laboratory determinations