CHAPTER III
RESEARCH METHODOLOGY

The study was to investigate the adherence to mineral and bone disorder clinical practice guideline in clinical parameters monitoring, using of phosphate binders, using of vitamin D_3 and achievement of clinical parameters in out-patient at nephrology unit, Srinagarind hospital. Furthermore the comparison of percentage of achievement target recommendation between adherent and non-adherent patients would be evaluated.

3.1 Study design

A retrospective cohort observational study was performed in patients with CKD in pre-dialysis and dialysis clinic, nephrology unit, Srinagarind hospital. The patients with CKD who visited the clinic between July 1, 2007 to September 30, 2007 were eligible to be included into the study.

3.1.1 Inclusion criteria

1) Age more than 18 years old.
2) CKD stage 3, 4 and 5.
2) Complete 12 months data before and after index date.

3.1.2 Exclusion criteria

1) The patient with primary hyperparathyroidism or thyroid neoplasia.
2) The patient received parathyroidectomy.
3) Kidney transplant patient.

3.2 Definition of terms used in this study

3.2.1 Index date

The date that patient with CKD was screened into the study which was during July 1, 2007 to September 30, 2007.

3.2.2 Preindex period

12 months before index date that the patient had been followed up at Srinagarind hospital.

3.2.3 Postindex period

12 months after index date that the patient had been followed up at pre-dialysis or dialysis clinic, nephrology unit, Srinagarind hospital.

3.2.4 Chronic kidney disease stage 3, 4 and 5

The identification of patient with CKD defined by K/DOQI clinical practice guideline for chronic kidney disease: evaluation, classification and stratification. (National Kidney Foundation, 2002)

Glomerular infiltration rate (GFR) was calculated from serum creatinine by using Modification of Diet in Renal Disease (MDRD) study equation as follow:

GFR (mL/min/1.73 m^2) =1.86 x (serum creatinine)$^{-1.154}$ x (age)$^{-0.203}$ (x 0.742 if female)

CKD stage 3 was the patient with moderate ↓ GFR or between 30-59 ml/min/1.73 m^2

CKD stage 4 was the patient with severe ↓ GFR or between 15-39 ml/min/1.73 m^2

CKD stage 5 was dialysis patient or the patient with GFR lower than 15 ml/min/1.73 m^2

3.2.5 Phosphate binders

Phosphate binders used at Srinagarind hospital; calcium carbonate ($CaCO_3$) 1 gram per tablet, $CaCO_3$ 1.5 grams per tablet, aluminum hydroxide ($Al(OH)_3$) gel or $Al(OH)_3$ 500 milligrams per tablet.

3.2.6 VitaminD_3

VitaminD_3 used at Srinagarind hospital; alfacalcidol 0.25 μg per tablet or calcitriol 0.25 μg per tablet.

3.2.7 Clinical parameters

Clinical parameters were serum corrected-calcium, serum phosphate, serum corrected-calcium x phosphate product (CaxP product) and serum PTH.

3.2.8 Mineral and bone disorder clinical practice guideline (MBD – CPG)

K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease 2003 composes of four parts;

Part 1: Measurement of clinical parameters

Part 2: Using of phosphate binders

Part 3: Using of vitaminD_3

Part 4: Target recommendations

Using of phosphate binders and vitaminD_3 were adjusted according to hospital drug list. The detail of guideline is described in 3.3.3

3.2.9 Adherence

Adherence is a term used to describe how well a physician is sticking to clinical practice guideline.

3.3 Instruments

3.3.1 Patient medical record

3.3.2 Laboratory result database in Srinagarind hospital

3.3.3 Mineral and bone disorder clinical practice guideline (MBD – CPG)

3.3.3.1 Measurement of clinical parameters

The frequency of clinical parameters monitoring for serum calcium, phosphate and PTH in the patient with CKD stage 3, 4 and 5 according to Table 2 were used to determine the adherence.

Table 2 Frequency of measurement of clinical parameters in patient with CKD

CKD stage	**Measurement of clinical parameters**	
	Serum PTH	**Serum calcium/ Serum phosphate**
3	Every 12 months	Every 12 months
4	Every 3 months	Every 3 months
5 or dialysis	Every 3 months	Every 1 months

3.3.3.2 Using of phosphate binders in CKD stage 3, 4 and 5

CKD stage 3

a) Discontinue phosphate binders, if serum phosphate is lower than 2.7 mg/ml

b) Continue treatment, if serum phosphate is 2.7-4.6 mg/ml

1b) No need to add phosphate binder, if no phosphate binder has been prescribed.

2b) Continue using phosphate binder, if phosphate binder has been prescribed.

c) If serum phosphate is more than 4.6 mg/ml, prescribed phosphate binder as follow;

1c) If CaxP product is lower than 55 mg^2/ml^2, use $CaCO_3$

2c) If CaxP product is more than 55 mg^2/ml^2, use $Al(OH)_3$

CKD stage 4

a) Discontinue phosphate binder, if serum phosphate is lower than 2.7 mg/ml

b) Continue treatment, if serum phosphate is 2.7-4.6 mg/ml

1b) No need to add phosphate binder, if no phosphate binder has been prescribed.

2b) Continue using phosphate binder, if phosphate binder has been prescribed.

c) If serum phosphate is more than 4.6 mg/ml, prescribed phosphate binder as follow;

1c) If CaxP product is lower than 55 mg^2/ml^2, use $CaCO_3$.

2c) If CaxP product is more than 55 mg^2/ml^2, use $Al(OH)_3$

. CKD stage 5

a) Discontinue phosphate binder, if serum phosphate is lower than 3.5 mg/ml.

b) Continue treatment, if serum phosphate is 3.5-5.5 mg/ml

1b) No need to add phosphate binder, if no phosphate binder has been prescribed.

2b) Continue using phosphate binder, if phosphate binder has been prescribed.

c) If serum phosphate is more than 5.5 mg/ml, prescribed phosphate binder as follow;

1c) If CaxP product is lower than 55 mg^2/ml^2, use $CaCO_3$.

2c) If CaxP product is lower than 55 mg^2/ml^2 but serum calcium is more than 10.2 mg/ml, use $Al(OH)_3$.

3c) If CaxP product is more than 55 mg^2/mL^2, use $Al(OH)_3$.

3.3.3.3 Using of vitaminD_3 in CKD stage3, 4 and 5

CKD stage 3

a) Continue treatment, if serum PTH is 35-70 pg/ml.

1a) No need to add vitaminD_3, if no vitaminD_3 has been prescribed.

2a) Continue using vitaminD_3, if vitaminD_3 has been prescribed.

b) If serum PTH is more than 70 pg/ml and/or serum calcium is lower than 9.5 mg/ml and/or serum phosphate is lower than 4.6 mg/ml, use alfacalcidol 0.25-1 μg OD or calcitriol 2-4 μg OD 3 times/week

c) If serum PTH is lower than 35 pg/ml or serum calcium is more than 9.5 mg/ml or serum phosphate is more than 4.6 mg/ml, decreased or discontinue vitaminD_3 dosing.

CKD stage 4

a) Continue treatment, if serum PTH is 70-110 pg/ml.

1a) No need to add vitaminD_3, if no vitaminD_3 has been prescribed.

2a) Continue using vitaminD_3, if vitaminD_3 has been prescribed.

b) If serum PTH is more than 110 pg/ml and/or serum calcium is lower than 9.5 mg/ml and/or serum phosphate is lower than 4.6 mg/ml, use alfacalcidol 0.25-1 μg OD or calcitriol 2-4 μg OD 3 times/week.

c) If serum PTH is lower than 70 pg/ml or serum calcium is more than 9.5 mg/ml or serum phosphate is more than 4.6 mg/ml, decreased or discontinue vitaminD$_3$ dosing.

CKD stage 5

a) Continue treatment, if serum PTH is 150-300 pg/ml.

1a) No need to add vitaminD$_3$, if no vitaminD$_3$ has been prescribed.

2a) Continue using vitaminD$_3$, if vitaminD$_3$ has been prescribed.

b) If serum PTH is more than 300 pg/ml, use calcitriol 2-4 μg OD 3 times/week.

c) If serum PTH is lower than 150 pg/ml or serum calcium is more than 10.2 mg/ml or serum phosphate is more than 6.0 mg/ml, decreased or discontinue vitaminD$_3$ dosing.

3.3.3.4 Target recommendations

K/DOQI target recommendations for clinical parameters; serum corrected-calcium, serum phosphate, serum CaxP product and serum PTH in the patient with CKD stage 3, 4 and 5 are described in Table 3.

Table 3 K/DOQI target recommendation of clinical parameters in patient with CKD

CKD stage	Serum phosphate (mg/dl)	Serum corrected-calcium (mg/dl)	Serum CaxP product (mg^2/dl^2)	Serum iPTH (pg/ml)
3	2.7–4.6	normal[a]	< 55	35-70
4	2.7–4.6	normal[a]	< 55	70-110
5	3.5-5.5	8.4–9.5	< 55	150-300

[a] normal value of serum calcium at Srinagarind hospital laboratory was 8.4-10.2 mg/dl

3.4 Methods

3.4.1 Inclusion of patient into the study

At index date (July 1, 2007 to September 30, 2007), the patients who met inclusion criteria were included into the study. They were classified into CKD stage 3, 4 and 5 according to K/DOQI clinical practice guideline. (National Kidney Foundation, 2002)

To determine CKD staging: calculated GFR at index date and 90 days pre and post index date were used to determine CKD stage. If they were not the same, the lowest GFR were used to determine staging.

3.4.2 Data collection

Part 1: Demographic data

Study number, hospital number, first name, surname, identical number, date of birth, address, gender, age, CKD stage, co-morbidity.

Part 2: Others

At index date (First visit): current medications, serum creatinine, serum albumin, serum calcium, serum phosphate, serum PTH.

Preindex period: serum creatinine, serum albumin, serum calcium, serum phosphate, serum PTH.

Postindex period (Every visit): current medications, serum creatinine, serum albumin, serum calcium, serum phosphate, serum PTH.

3.4.3 Data analysis

Clinical parameters monitoring

Adherence to clinical parameters monitoring in each patient was determined at first visit after the index date and every visit during 12 months of postindex period. In each visit, the frequency of monitoring for serum calcium, phosphate and PTH were determined for adherence according to MBC – CPG. Then at the end of 12 months of postindex period the percentage of adherence to clinical parameters monitoring (% Adherence) was evaluated as follow:

$$\%\text{Adherence} = \frac{\text{No of adherence to clinical parameters monitoring visit}}{\text{Total visit}} \times 100$$

Using of phosphate binders

Adherence to using of phosphate binders in each patient was determined at first visit after index date and every visit during 12 months of postindex period. In each visit, using of phosphate binders was determined for adherence according to MBD – CPG. Then at the end of 12 months of postindex period, the percentage of adherence to using of phosphate binders (% Adherence) was calculated as follow:

$$\%\text{Adherence} = \frac{\text{No of adherence to using of phosphate binders visit}}{\text{Total visit}} \times 100$$

Note: Only the visits that had both calcium and phosphate monitoring were evaluated.

Using of vitaminD_3

Adherence to using of vitaminD_3 in each patient was determined at first visit after index date and every visit during 12 months of postindex period. In each visit, using of vitaminD_3 was determined for adherence according to MBD – CPG. Then at the end of 12 months of postindex period, the percentage of adherence to using of vitaminD_3 (% Adherence) was calculated as follow:

$$\%\text{Adherence} = \frac{\text{No of adherence to using of vitamin}D_3\text{visit}}{\text{Total visit}} \times 100$$

Note: Only the visits that had all of calcium, phosphate and PTH monitoring were evaluated.

Achievement of K/DOQI target recommendations

Achievement of clinical parameters according to K/DOQI target recommendations was determined at first visit after index date, during 12 months of postindex period that had laboratory test and at the end of the study. The percentage of achievement K/DOQI target recommendations (% Achievement) was calculated as follow:

$$\%\text{Achievement} = \frac{\text{No of the achievement of target recommendations visit}}{\text{Total visit}} \times 100$$

Note: Only the visits that had calcium, phosphate or PTH monitoring were monitored.

3.5 Statistical analysis

The results were analyzed by using SPSS version 10. Descriptive statistics were used to present the data. Gender, CKD stage, co-morbidity, dialysis or pre-dialysis and medications at index date were described as percentage. Continuous variables were presented in mean (SD) for normal distribution data or median (IQR) for skewed data which were age, serum creatinine, GFR, serum albumin, serum calcium, serum phosphate, serum PTH, calculated CaxP product, %adherence and %achievement of MBD - CPG. Finally Chi-square test or Fisher-exact test would be used to compare the percentage of achievement of target recommendations between adherent and non-adherent patients.

3.6 Ethical approval

Prior to initiation, the study was reviewed and approved by the Ethics Committee of Khon Kaen University.