Prevalence of potassium, phosphate and acid-base abnormalities among CKD patients in central northeast of Thailand

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Background   : *Hyperkalemia, hyperphosphatemiaand metabolic acidosis are common complications among chronic kidney disease (CKD) patients. However, there were several reports of hypokalemia in population resides in the northeast of Thailand. The prevalence of electrolyte imbalance in CKD patients in this region was still unknown.*

Objective   : *To study the prevalence of potassium, phosphate and acid-base imbalance in CKD patients in the central northeast of Thailand.*

Design   : *Cross-sectional descriptive study*

Setting   : *Roi-et, Mahasarakham, Khonkaen and Kalasin Provincial public health offices.*

Material and Method : *We used specific My SQL query command for retrieving laboratory data between Jan 1ˢᵗ - Dec 31ˢᵗ, 2014 from the databases of four provincial public health offices regarding ICD 9 and 10 of pre-dialysis CKD codes.*

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Result   :   *In total, databases of 31,180 CKD patients were retrieved. The mean estimated glomerular filtration rate (eGFR), serum potassium, phosphate and bicarbonate were 34.7 ± 24.6 ml/min/ 1.73 m^2, 4.2 ± 0.7 mEq/L, 4.1 ± 1.6 mg/dL and 24.2 ± 4.3 mEq/L, respectively. CKD 5 had the highest prevalence of hyperkalemia, hyperphosphatemia and metabolic acidosis (39.9%, 41.5% and 40.8%, respectively). The overall prevalences of hyperkalemia and hyperphosphatemia were higher than hypokalemia and hypophosphatemia (30.1% and 30% vs.10.6% and 7%); however, the prevalence of metabolic alkalosis was higher than metabolic acidosis (30.9% vs. 26.1%). The eGFR correlated positively with serum bicarbonate (r = 0.30, p <0.01) and negatively with serum potassium and phosphate (r = -0.19 and - 0.29, p <0.01).*

Conclusion   :   *Hyperkalemia and hyperphosphatemia were major metabolic complications among CKD patients in the central northeast of Thailand. Contrary to our knowledge, the prevalence of metabolic alkalosis was higher than metabolic acidosis in these patients.*

Keywords   :   *Chronic kidney disease (CKD), hypokalemia, hypophosphatemia, metabolic alkalosis, electrolyte imbalance.*

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ที่มา : *ภาวะโปแตสเซียมและฟอสเฟตสูงและเลือดเป็นกรดเป็นภาวะแทรกซ้อนที่พบบ่อยในผู้ป่วยโรคไตเรื้อรัง แต่จากข้อมูลก่อนหน้าพบว่าประชากรในภาคตะวันออกเฉียงเหนือมีความชุกของภาวะโปแตสเซียมต่ำสูง ปัจจุบันยังไม่มีข้อมูลความชุกของภาวะเกลือแร่ผิดปกติในผู้ป่วยโรคไตเรื้อรังในพื้นที่ดังกล่าว*

วัตถุประสงค์ : *เพื่อศึกษาความชุกของภาวะระดับโปแตสเซียม, ฟอสเฟตและสมดุลกรดด่างผิดปกติในผู้ป่วยโรคไตเรื้อรังในพื้นที่ภาคตะวันออกเฉียงเหนือตอนกลาง*

รูปแบบการวิจัย : *การศึกษาวิจัยเชิงพรรณนา ณ จุดเวลาใดเวลาหนึ่ง*

สถานที่ทำการศึกษา : *จังหวัดร้อยเอ็ด, มหาสารคาม, ขอนแก่นและกาฬสินธุ์*

ตัวอย่างและวิธีการศึกษา : *ข้อมูลผลตรวจทางห้องปฏิบัติการของผู้ป่วยโรคไตเรื้อรังที่มารับบริการในสถานพยาบาลของรัฐช่วงวันที่ 1 มกราคมถึง 31 ธันวาคม 2557 จากฐานข้อมูล 43 แฟ้มของสำนักงานสาธารณสุขจังหวัดทั้ง 4 แห่ง ถูกดึงออกมาโดยการสร้างคำสั่ง My SQL สืบค้นข้อมูลตามรหัส ICD 9 และ 10 ของผู้ป่วยโรคไตเรื้อรังระยะก่อนบำบัดทดแทนไต*

ผลการศึกษา : *จากข้อมูลผู้ป่วย 31,180 ราย พบว่าค่าเฉลี่ยของการทำงานของไต (eGFR), โปแตสเซียม, ฟอสเฟตและไบคาร์บอเนตในเลือด 34.7 ± 24.6 ml/min/1.73m^2, 4.2 ± 0.7 mEq/L, 4.1 ± 1.6 mg/dL และ 24.2 ± 4.3 mEq/L ตามลำดับ ผู้ป่วยโรคไตเรื้อรังระยะที่ 5 มีความชุกของภาวะโปแตสเซียมและฟอสเฟตสูงและเลือดเป็นกรดสูงที่สุดเมื่อเทียบกับระยะอื่น (39.9%, 41.5% และ 40.8% ตามลำดับ) เมื่อวิเคราะห์ในภาพรวมพบว่าความชุกของภาวะโปแตสเซียมและฟอสเฟตสูงมีมากกว่าโปแตสเซียมและฟอสเฟตต่ำ (30.1% และ 30% กับ 10.6% และ 7%) อย่างไรก็ตามพบว่าความชุกของภาวะเลือดเป็นด่างสูงกว่าเลือดเป็นกรด (30.9% กับ 26.1%) eGFR มีความสัมพันธ์เชิงบวกกับระดับไบคาร์บอเนต (r = 0.30, p <0.01) และมีความสัมพันธ์เชิงลบกับโปแตสเซียมและฟอสเฟต (r = -0.19 และ -0.29, p <0.01)*

สรุป	:	*ภาวะโปแตสเซียมและฟอสเฟตสูงยังเป็นภาวะแทรกซ้อนที่สำคัญ ในผู้ป่วยโรคไตเรื้อรังในเขตพื้นที่ภาคตะวันออกเฉียงเหนือตอนกลาง อย่างไรก็ตามกลับพบภาวะเลือดเป็นด่างสูงกว่าภาวะเลือดเป็นกรดใน ผู้ป่วยกลุ่มนี้*
คำสำคัญ	:	*โรคไตเรื้อรัง, ภาวะโปแตสเซียมในเลือดต่ำ, ภาวะฟอสเฟตในเลือดต่ำ, ภาวะเลือดเป็นด่าง, ภาวะระดับเกลือแร่ในเลือดผิดปกติ.*

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Chronic kidney disease (CKD) is a major health burden in Thailand. According to Thai SEEK study, the overall prevalence of CKD was about 17.5%. [1] This number was 2.5% higher than that of the United States in 2007 - 2012.[2] Regionally, the northeast of Thailand has the largest size of population in the country. And CKD prevalence in this region was 22.2%, the second most prevalent after Bangkok.[1] Therefore, CKD management is an important health care issue in this region.

Electrolyte imbalance is one of major complications among CKD patients. To our knowledge, almost CKD patients, especially in advanced stage (CKD 4 - 5); have some specific abnormal electrolyte patterns such as hyperkalemia, hyperphosphatemia and metabolic acidosis. A number of CKD guidelines were developed to overcome these problems. However, most guidelines were based on studies from developed countries; hence, some recommendations were not compatible with situations in developing countries. Regional database would represent the characteristics of each population and would be best resource for the development of the local guidelines.

From several reports, the population in the northeastern region has its unique feature of electrolyte disorders both in blood and in urine such as hypokalemia[3, 4], low urine potassium[4], hypocitraturia, hypomagnesemia,[5] etc. These disorders are related to many diseases which are most prevalent in this region such as renal calculi and sudden unexplained death syndrome.[3] Most previous studies were done in patients who had renal calculi or history of sudden unexplained death syndrome in family, but the data in chronic kidney disease are still unknown.

Material and Method

We conducted a cross-sectional, obser-vational study in collaboration with four provincial public health offices (Roi-et, Mahasarakham, Khonkaen and Kalasin). The programmer developed specific My SQL (My Structured Query Language) query command regarding ICD 9 and 10 codes of pre-dialysis CKD. This command was designed to retrieve all pre-dialysis CKD cases following KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease definition and registered as out patients in the databases of the 4 provincial public health offices (43 files database) from January 1st - December 31st, 2014 with age over 18 years old. Cases that had been diagnosed acute kidney injury or undergone renal replacement therapy were excluded. Because of the database design, we had accessed to only specific laboratory results including serum creatinine, potassium, phosphate bicarbonate and hemoglobin. Besides the laboratory data, gender and age were also collected for calculating estimated glomerular filtration rate (eGFR) using CKD-EPI formula.

Definition

Pre-dialysis CKD patients were categorized into 5 stages according to the KDIGO 2012 Classification[6]: CKD stage 1, eGFR $\geq$ 90 ml/min/1.73m^2; CKD stage 2, eGFR 60 - 89 ml/min/1.73 m^2; CKD stage 3, eGFR 30 - 59 ml/min/1.73m^2; CKD stage 4, eGFR 15-29 ml/min/1.73m^2 and CKD stage 5, eGFR $\leq$ 15 ml/min/1.73m^2. eGFR was calculated from serum creatinine, age, gender and race according to CKD-EPI formula (equation 1 - 4).

Female:serum creatinine ≤ 0.7 mg/dL

eGFR = 144 × (SCr/0.7)$^{-0.329}$ × 0.993^{Age} [×1.159 if black]..........………1

Female: serum creatinine > 0.7 mg/dL

eGFR = 144 × (SCr/0.7)$^{-1.209}$ × 0.993^{Age} [×1.159 if black]….…………2

Male: serum creatinine ≤ 0.9 mg/dL

eGFR = 141 × (SCr/0.9)$^{-0.411}$ × 0.993^{Age} [×1.159 if black]….…………3

Male: serum creatinine > 0.9 mg/dL

eGFR = 141 × (SCr/0.9)$^{-1.209}$ × 0.993^{Age} [× 1.159 if black]….…………4

Hyperkalemia was defined as serum potassium >4.5 mEq/L.

Hypokalemia was defined as serum potassium <3.5 mEq/L.

Hyperphosphatemia was defined as serum phosphate >4.5 mg/dL.

Hypophosphatemia was defined as serum phosphate < 2.5 mg/dL.

Metabolic acidosis was defined as serum bicarbonate < 22 mEq/L.

Metabolic alkalosis was defined as serum bicarbonate >26 mEq/L.

Anemia was defined as hemoglobin < 12 g/dL. (Regarding KDIGO 2011 guideline for anemia in chronic kidney disease[7], anemia was defined by hemoglobin level < 12 g/dL in female and < 13 g/dL in male. We selected hemoglobin level < 12 g/dL to diagnose anemia in both sex because of difficulty in data reclassification. We did not use therapeutic goal of hemoglobin level because erythropoietin was not provided to all anemic CKD patients in this area and this study did not aim to evaluate the treatment outcome)

Statistical analysis

Age and laboratory results were expressed as mean values ± standard deviation. The prevalence of each electrolyte disorders was presented in percentage. One-way ANOVA was employed to compare laboratory results in each CKD staging. As for multiple comparisons, Tukey method was used due to unequal sample size in each group. Pearson correlation coefficients (r) and their significance were calculated between eGFR and each laboratory result. A p-value ofless than or equal to 0.05 was considered statistical significance. Microsoft Excel 2010 and IBM SPSS Statistics 20 (IBM Corp, Armonk, NY, USA) were used for all statistical analyses.

Results

Demographic data (Table 1)

In total, data of 39,441 patients were retrieved after query process. From these, 8,261cases were excluded due to extremely high and low eGFR values, and 31,180 were eligible for analysis. Most of them were female (55.7%) with their mean age of 64.1 ± 12.3 years and classified into CKD 4. Mean eGFR, serum potassium, phosphate, bicarbonate and hemoglobin was 34.7 ± 24.6 ml/min/1.73m^2, 4.2 ± 0.7 mEq/L, 4.1 ± 1.6mg/dL, 24.2 ± 4.3 mEq/L and 10.3 ± 2.3 g/dL, respectively.

Laboratory data analysis

The overall prevalence of hyperkalemia $vs.$ hypokalemia, metabolic acidosis $vs.$ metabolic alkalosis, hyperphosphatemia $vs.$ hypophosphatemia and anemia was 30.1% $vs.$ 10.6%, 26.1% $vs.$ 30.9%, 30% $vs.$ 7% and 73.7%, respectively. The CKD 5 had the highest prevalence of hyperkalemia,

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hyperphosphatemia, metabolic acidosis and anemia (Table 2). Comparison of serum potassium, bicarbonate and hemoglobin at various CKD stage (CKD 1 - 2 *vs.* CKD 3, CKD 4 and CKD 5; CKD 3 *vs.* CKD 4 and CKD 5; CKD 4 *vs.* CKD 5) showed significantly different. However, serum phosphate level in CKD 1 - 2 was comparable to CKD3 and CKD 4 (Figure 1).

Table 1. Demographic data.

Characteristics	Result (*n* = 31,180)
Sex, number (%)	
Male	13,807 (44.3%)
Female	17,373 (55.7%)
Age, years	64.1 ± 12.3
CKD staging, number (%)	
CKD 5	7,835 (25.1)
CKD 4	9,327 (30.0)
CKD 3	8,411(27.0)
CKD 1-2	5,607 (17.9)
eGFR, ml/min/$1.73m^2$	34.7 ± 24.6
Potassium, mEq/L	4.2 ± 0.7
Phosphate, mg/dL	4.1 ± 1.6
Bicarbonate, mEq/L	24.2 ± 4.3
Hemoglobin, g/dL	10.3 ± 2.3

Table 2. Prevalence of electrolyte abnormality, classified by CKD stage.

| Laboratory data	Prevalence (%)				
	CKD 1-2	CKD 3	CKD 4	CKD 5	overall
Potassium (mEq/L)					
Hypokalemia (<3.5)	12.4	12.4	9.7	9.7	10.6
Normal (3.5 - 4.5)	73.6	64.8	60.3	50.4	59.3
Hyperkalemia (>4.5)	14.0	22.8	30.0	39.9	30.1
Bicarbonate (mEq/L)					
Acidosis (<22)	6.9	11.5	20.0	40.8	26.1
Normal (22 - 26)	38.4	45.4	50.5	38.1	43.0
Alkalosis (>26)	54.7	43.1	29.5	21.1	30.9
Phosphate (mg/dL)					
Hypophosphatemia (<2.5)	14.3	9.9	3.9	7.6	7.0
Normal (2.5 - 4.5)	85.7	81.7	80.4	50.9	63.0
Hyperphosphatemia (>4.5)		8.4	15.7	41.5	30.0
Hemoglobin (g/dL)					
Anemia (<12)	32.4	56.5	76.5	94.1	73.7
Normal (≥12)	67.6	43.5	23.5	5.9	26.3
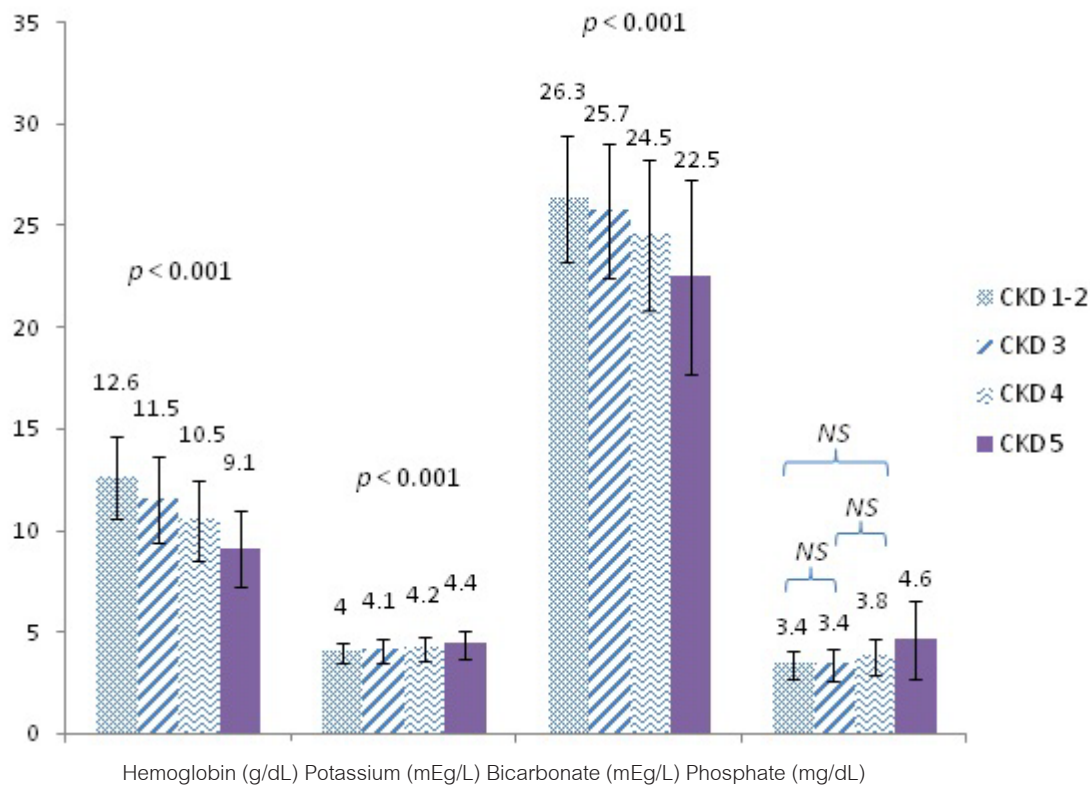
Figure 1. Comparison of laboratory value at various CKD stage.
        NS = no statistical difference between groups.

Correlation of eGFR and laboratory value

The eGFR had positive correlation with serum bicarbonate and hemoglobin level (r = 0.30 and 0.53, p <0.01) and correlated negatively with serum potassium and phosphate (r = -0.19 and -0.29, p <0.01).

Discussion

This was the first study that explored the actual prevalence of electrolyte imbalance among CKD patients who resided in the central northeast of Thailand. Even though this region is known for having high prevalence of hypokalemia[3, 4, 8], the majority of potassium imbalance in CKD patients was still hyperkalemia. The present result also confirmed that hyperphosphatemia and anemia were major complications in CKD patients in the northeastern region of Thailand. However, metabolic acidosis was not the main acid-base imbalance as in theory.

In addition to a decrease in eGFR and disturbances in renal handling of potassium, treatment with RAAS inhibitors for managing CKD progression is linked with an increased risk of hyperkalemia. This reason explained why the prevalence of hypokalemia in CKD patients was not as high as expected. All CKD patients registered with the provincial public health office were managed following the up-to-date CKD guidelines; therefore, RAAS inhibitors were generally prescribed for these patients. Nevertheless, the prevalence of hypokalemia among CKD patients in the present study seemed to be higher than others. Compared to Wang HH *et al.*, the prevalence of

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hypokalemia (serum potassium < 3.5 mEq/L) in CKD 4 in this study was higher (5.6% *vs.* 9.7%)[9]. Similar results were shown when compared to the study of Sarafidis PA *et al.* (0.4% *vs.* 9.7%)[10]. Moreover, when compared to community-based (non CKD) population[11], the overall prevalence in present study was still higher (2.7% *vs.* 10.6%). This finding might be correlated with previous evidence. Hypotheses of low potassium intake[3, 12], excessive sweating[3], hypomagnesemia[5, 13] and hereditary disorders such as renal tubular acidosis[14] and hypokalemic periodic paralysis were proven in patients with renal calculi and normal population in this region. The mechanism of hypokalemia among northeastern CKD patients should be further explored.

Contrary to our knowledge, the overall prevalence of metabolic alkalosis was higher than metabolic acidosis in this region. Even it tended to be much more metabolic acidosis prevalence in advanced CKD patients; this finding was lower than other studies. Regarding the study of Raphael KL *et al.*, the prevalence of low bicarbonate (serum bicarbonate < 22 mEq/L) by CKD stage was 7% for stage 2, 13% for stage 3, and 37% for stage 4 CKD.[15] But when compared to community-based study[16], the prevalences of metabolic acidosis and metabolic alkalosis in this study were both higher (8% and 9% *vs.* 26.1% and 30.9%, respectively). We proposed three mechanisms to explain the lower metabolic acidosis prevalence. First, the northeastern area was covered by arid climate. Extreme dry and high temperature and agricultural life style caused excessive sweating. Moreover, shortage of water supply in some areas caused dehydration and led to contraction alkalosis. Second, the routine prescription

of bicarbonate salts and diuretics without laboratory checkup occurred in some medical services. Third, hypokalemia itself could increase and maintain metabolic alkalosis.

Hyperphosphatemia was an important complication of CKD. According to our result, the prevalence of hyperphosphatemia classified by stage of CKD was rather lower than the previous study. Ramos AM *et al.* found hyperphosphatemia in 25% of CKD 4 and 47% of CKD 5 patients[17] which was higher than 15.7% and 41.5% of our CKD 4 and CKD 5 patients. However, we could not find the prevalence of hyperphosphatemia and hypophosphatemia in general population to compare with our data. Two hypotheses explained the lower prevalence of hyperphosphatemia and unexpected hypophosphatemia prevalence were proposed. First, most population had lower protein and phosphate intake according to their local life style. Second, the routine prescription of calcium carbonate occurred in some areas.

Unsurprisingly, the extremely high prevalence of anemia was existing in our region. Compared to the United States data, our result showed twice higher prevalence in all CKD stages.[18] Besides anemia from CKD, the northeast of Thailand was well known for its high prevalence of thalassemia[19, 20] and iron deficiency.[21] Thus, to explore the actual mechanism of anemia among CKD patients in this region was valuable for national health policy and guiding the provision of erythropoietin.

Conclusion

Hyperkalemia and hyperphosphatemia was major metabolic complication among CKD patients in

the central northeast of Thailand. Contrary to our knowledge, the prevalence of metabolic alkalosis was higher than metabolic acidosis in these patients. Anemic prevalence in the region seemed to be higher than other areas according to multifactor. More advanced CKD stage tended to have higher metabolic derangement.

Acknowledgement

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