Protein-bound Uremic Toxins Lowering Effect of Sevelamer in Pre-dialysis Chronic Kidney Disease Patients with Hyperphosphatemia: A Randomized Controlled Trial

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การศึกษาประสิทธิภาพของยาเซวาเลเมอร์ต่อการลดลงของสารพิษยูรีเมียที่จับกับโปรตีนในผู้ป่วยไตวายเรื้อรังที่มีระดับฟอสเฟตในเลือดสูง

น.ส.กุลยา ตรรกวาทการ

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรดุษฎีบัณฑิต
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กุลยา ตรรกวาทการ : การศึกษาประสิทธิภาพของยาเซวาเลเมอร์ต่อการลดลงของสารพิษยูรีเมียที่จับกับโปรตีนในผู้ป่วยไตวายเรื้อรังที่มีระดับฟอสเฟตในเลือดสูง. (Protein-bound Uremic Toxins Lowering Effect of Sevelamer in Pre-dialysis Chronic Kidney Disease Patients with Hyperphosphatemia: A Randomized Controlled Trial) อ.ที่ปรึกษาหลัก : รศ. พญ.ปวีณา สุสัณฐิตพงษ์, อ.ที่ปรึกษาร่วม : ผศ. นพ.อัษฎาศ์ ลีฬหวนิชกุล

ที่มาของปัญหางานวิจัย พีครีซิลซัลเฟตและอินดอกซินซัลเฟตมีความสัมพันธ์กับโรคหัวใจและหลอดเลือดและอัตราการเสียชีวิตในผู้ป่วยโรคไตเรื้อรังอย่างมาก การศึกษานี้เป็นการศึกษาแรกที่เปรียบเทียบประสิทธิภาพของยาเซวาเลเมอร์และแคลเซียมคาร์บอเนตต่อการลดระดับพีครีซิลซัลเฟตและอินดอกซิลซัลเฟตในผู้ป่วยโรคไตเรื้อรังที่มีระดับฟอสเฟตในเลือดสูง

ระเบียบวิธีการวิจัย ผู้ป่วยโรคไตเรื้อรัง 40 ราย จะได้รับการแบ่งกลุ่มโดยการสุ่ม เพื่อรับยาจับฟอสเฟตเป็นเซวาเลเมอร์ 2,400 มิลลิกรัมหรือแคลเซียมคาร์บอเนต 1,500 มิลลิกรัม เป็นเวลา 24 สัปดาห์ มีการตรวจวัดระดับของพีครีซิลซัลเฟต อินดอกซิลซัลเฟต ไฟโบรบลาสต์โกรธแฟกเตอร์ 23 คลอเลสเตอรอล และซี-รีแอกทีฟโปรตีน ที่เวลาตั้งต้น 12 และ 24 สัปดาห์ โดยมีผลลัพธ์หลักคือการเปลี่ยนแปลงของระดับพีครีซอล

ผลการศึกษา หลังการรักษา 24 สัปดาห์ ผู้ป่วยที่ได้รับยาเซวาเลเมอร์มีการลดลงของระดับพีครีซิลซัลเฟตอย่างมีนัยสำคัญทางสถิติเมื่อเปรียบเทียบกับผู้ป่วยที่ได้รับแคลเซียมคาร์บอเนต (ค่าเฉลี่ยของความแตกต่าง -5.61 มิลลิกรัม/ลิตร; ช่วงความเชื่อมั่นร้อยละ 95 เท่ากับ -11.01 ถึง -0.27 มิลลิกรัม/ลิตร; p=0.04) และมีการลดลงของระดับไฟโบรบลาสต์โกรทแฟคเพอร์ 23 และแอลดีแอลคลอเลสเตอรอลอย่างมีนัยสำคัญทางสถิติเมื่อเปรียบเทียบกับกลุ่มที่ได้รับแคลเซียมคาร์บอเนต ไม่พบการเปลี่ยนแปลงของระดับอินดอกซิลซัลเฟตและซี-รีแอกทีฟโปรตีน การทำงานของไตและความแข็งของหลอดเลือดแดงในผู้ป่วยทั้งสองกลุ่ม

สรุป ยาเซเวลาเมอร์สามารถลดระดับของพีครีซิลซัลเฟต ไฟโบรบลาสต์โกรทแฟคเพอร์ 23 และระดับคลอเลสเตอรอล ในผู้ป่วยโรคไตเรื้อรังที่มีระดับฟอสเฟตในเลือดสูง ทำให้ยาเซเวลาเมอร์อาจเป็นการรักษาที่ช่วยลดความเสี่ยงในการเกิดโรคหัวใจและหลอดเลือดในผู้ป่วยโรคไตเรื้อรังได้

สาขาวิชา อายุรศาสตร์ ลายมือชื่อนิสิต .....
ปีการศึกษา 2563 ลายมือชื่อ อ.ที่ปรึกษาหลัก .....
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Kullaya Takkavatakarn : Protein-bound Uremic Toxins Lowering Effect of Sevelamer in Pre-dialysis Chronic Kidney Disease Patients with Hyperphosphatemia: A Randomized Controlled Trial. Advisor: Assoc. Prof. PAWEENA SUSANTITAPHONG, Ph.D. Co-advisor: Asst. Prof. ASADA LEELAHAVANICHKUL, Ph.D.

Background: P-cresyl sulfate and indoxyl sulfate are strongly associated with cardiovascular events, and all-cause mortality in chronic kidney disease (CKD). This study was conducted to compare the effects between sevelamer and calcium carbonate on protein-bound uremic toxins in pre-dialysis CKD patients with hyperphosphatemia.

Methods: After 2 weeks of the run-in period, 40 pre-dialysis CKD patients with persistent hyperphosphatemia were randomly assigned to receive either daily 2,400 mg of sevelamer or 1,500 mg of calcium carbonate for 24 weeks. Serum p-cresyl sulfate, indoxyl sulfate, fibroblast growth factor 23 (FGF23), lipid profiles, and high sensitivity C-reactive protein (hs-CRP) were evaluated. The primary endpoint was to evaluate the effect of sevelamer on p-cresyl sulfate level.

Results: After 24 weeks, a significant decrease of serum p-cresyl sulfate was observed in sevelamer compared with calcium carbonate therapy (mean difference -5.61 mg/L; 95% CI -11.01 to -0.27 mg/L; p=0.04). Sevelamer had obvious effects in lowering FGF23 (p= 0.007) and LDL-cholesterol levels (p<0.001) but did not affect serum indoxyl sulfate and hs-CRP levels.

Conclusions: Sevelamer could effectively reduce serum p-cresyl sulfate, FGF23 levels, and improve lipid profiles in pre-dialysis CKD patients with hyperphosphatemia. Our data suggest the additional benefits of sevelamer over calcium-based phosphate binder in cardiovascular protection.

Field of Study: Medicine
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Student's Signature .....
Advisor's Signature .....
Co-advisor's Signature .....

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Kullaya Takkavatakarn

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CHAPTER I

BACKGROUND AND RATIONALE

Background

Chronic kidney disease (CKD) is one of the most important global health problems which significantly increases cardiovascular risk and mortality[1]. Several risk factors are proposed including traditional risk factors such as diabetes, hypertension, dyslipidemia, and uremic-related risk factors including anemia, mineral and bone disorders, inflammation, oxidative stress, and uremic toxins[2].

Impairment of renal function in CKD results in the accumulation of uremic toxins which can be classified into 3 groups based on their molecular weight and plasma protein affinity: 1) small molecules (< 500 Dalton), 2) middle molecules (> 500 Dalton), and 3) protein-bound uremic toxins which are small molecular weight substances but have high binding capacity to large protein, particularly albumin[3]. Indoxyl sulfate and p-cresyl sulfate are the two most commonly studied protein-bound uremic toxins. Both substances originated from amino acid metabolism of colonic bacteria. The chronically heightened levels of indoxyl sulfate and p-cresyl sulfate are associated with multiple adverse outcomes, including enhanced progression of renal failure, increased cardiovascular disorders and mortality, and elevated all-cause mortality in both non-dialysis and dialysis CKD[4]. Because of their binding affinity to albumin, protein-bound uremic toxins could not be effectively removed by conventional hemodialysis or peritoneal dialysis. Certain non-dialysis strategies such as the restriction of protein diet and manipulation of gut microbiota have been conducted to lower serum indoxyl sulfate and p-cresyl sulfate levels. However, the effectively therapeutic reduction of these toxins is still limited.

Sevelamer, an anion exchange resin, is a widely used non-calcium-based phosphate binder which can bind other anionic substances. In addition to the phosphate-binding effect, sevelamer seems to exert a pleiotropic effect including lowering lipid profile and inflammatory markers. In this study, we aim to examine the protein-bound uremic toxins lowering effect of sevelamer in CKD patients with hyperphosphatemia.

Research question

Primary research question

What effect does sevelamer have on serum p-cresyl sulfate in non-dialysis chronic kidney disease patients with hyperphosphatemia?

Secondary research question

- What effect does sevelamer have on serum indoxyl sulfate in non-dialysis chronic kidney disease patients with hyperphosphatemia?
- Does sevelamer reduce inflammation in chronic kidney disease patients?
- Can sevelamer prevent renal progression in chronic renal disease patients?

Objectives

- To compare the effect of sevelamer and calcium carbonate on serum p-cresyl sulfate levels in pre-dialysis chronic kidney disease patients with hyperphosphatemia
- To compare the effect of sevelamer and calcium carbonate on serum indoxyl sulfate levels in pre-dialysis chronic kidney disease patients with hyperphosphatemia
- To study the effect of sevelamer on inflammatory markers in pre-dialysis chronic kidney disease patients
- To study the effect of sevelamer on renal progression in pre-dialysis chronic kidney disease patients

Hypothesis

- Sevelamer can reduce serum p-cresyl sulfate and indoxyl sulfate levels in pre-dialysis chronic kidney disease patients with hyperphosphatemia.
- Sevelamer can reduce inflammatory markers in pre-dialysis chronic kidney disease patients.

- Reduction of serum p-cresyl sulfate and indoxyl sulfate can slow renal progression in pre-dialysis chronic kidney disease patients.

Research design

This study is a therapeutic experimental single-centered, open-label, prospective, randomized controlled trial comparing sevelamer and calcium carbonate in pre-dialysis chronic kidney disease with hyperphosphatemia.

Conceptual framework

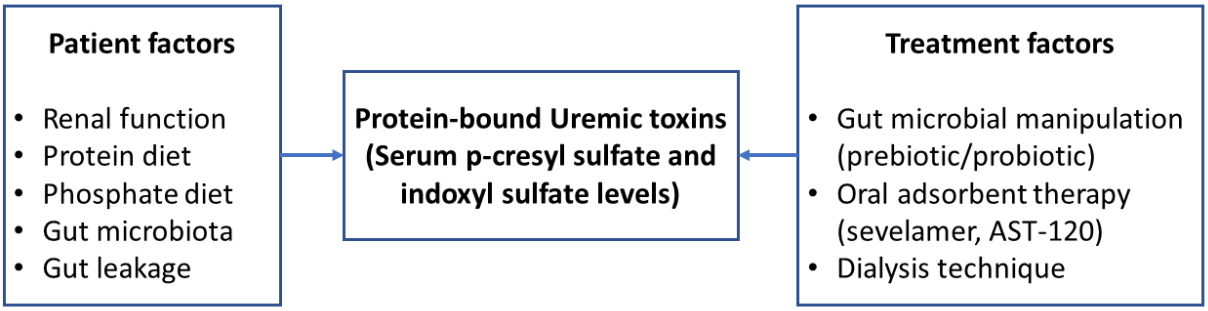

Figure 1 Conceptual framework of factors affecting protein-bound uremic toxins in pre-dialysis chronic kidney disease patients with hyperphosphatemia

CHAPTER II
REVIEW OF LITERATURE

Chronic kidney disease (CKD) is a clinical syndrome which the structure or function of the kidney is persistently abnormal for more than 3 months. CKD is defined as a decrease in glomerular filtration rate (GFR) less than 60 mL/min/1.73m^2, or presence of evidence of renal structure abnormalities including persistent albuminuria (≥ 30 mg in 24 hours), urine sediment, electrolyte and other tubular disorders, changes in renal imaging, histological changes in kidney biopsy, and previous kidney transplantation[5]. CKD is categorized into five and three stages according to GFR and albuminuria, respectively, as shown in Tables 1 and 2.

CKD is a common public health problem. The estimated global prevalence of CKD was about 3-18% of populations vary by country[6]. In Thailand, the estimated prevalence of CKD was 8-13.2%[7]. CKD is associated with accelerated cardiovascular risk and mortality. The relative risk of cardiovascular mortality in patients with CKD compared with those without CKD was 2.19 (95% CI 1.76-2.73)[8]. In addition, the risks of cardiovascular events and mortality are significantly increasing along with the decline of renal function[9]. Data from the US Renal Data System (USRDS) annual report 2010 showed that patients with CKD had a much larger burden of CVD than did patients without CKD and that the prevalence of each category of CVD was higher in the more advanced stages of CKD relative to the less advanced. After adjustment for age, sex, and race, any CVD was present in 37.5% of patients without CKD compared with 63.4% of patients with stages 1-2 CKD, 66.6% of patients with stage 3 CKD, and 75.3% of patients with stages 4-5 CKD (Figure 2). In addition, the survival probability following a first diagnosis of a cardiovascular condition or event was lower for patients with CKD than for those without. In the case of coronary artery disease (CAD), the adjusted two-year survival probability among those without CKD (0.81) was comparable to the 11-month survival probability of patients with stage 3 CKD and the 5-month survival probability of patients with stages 4-5 CKD[10].

Table 1 CKD staging by Kidney Disease Initiatives Global Outcomes (KDIGO) 2012

Stage	GFR (mL/min/1.73m^2)
G1	≥ 90
G2	60-89
G3a	45-59
G3b	30-44
G4	15-29
G5	< 15

Abbreviation: GFR: glomerular filtration rate

Table 2 Albuminuria categories in CKD

Category	Albumin excretion rate (mg/24 hours)	Terms
A1	< 30	Normal to mildly increased
A2	30-300	Moderately increased
A3	> 300	Severely increased

Figure 2 Adjusted prevalence of common cardiovascular diseases by CKD status and stage, USRDS Annual data report 2018.

The higher risk of developing cardiovascular disease in CKD patients could not be explained only by traditional risk factors, such as hypertension, dyslipidemia, diabetes and smoking. The additional risk factors including novel risk factors such as oxidative stress, inflammation, endothelial dysfunction, and uremic specific risk factors such as uremic toxin accumulation from decreased renal excretion, anemia, and mineral bone disorder (CKD-MBD), are also proposed.

Uremic toxins

Uremic toxins are compounds that are usually filtered and excreted by the kidneys. In the setting of CKD, these compounds accumulate and exert their uremic effects on various systems. According to the database of the European Uremic Toxin (EuTOX) working group, there are at least 152 uremic toxins which can be classified based on their molecular weight and plasma protein affinity into three major groups[3]:

1) Small molecules (< 500 Dalton) which are water-soluble and easily pass any dialysis filter
2) Middle molecules (> 500 Dalton) for which passage through a dialysis filter is limited and determined by membrane properties
3) Protein-bound uremic toxins which are small molecular weight substances but have a high binding capacity to large protein, particularly albumin

The uremic toxins in CKD patients can accumulate through several mechanisms as following[11]

1) Decreased renal excretion
2) Increased synthesis from endogenous metabolism
3) Increased synthesis from intestinal dysbiosis including gut-derived uremic toxins such as p-cresyl sulfate and indoxyl sulfate.
4) Increased dietary intake, for example phosphate, and L-carnitine.

Uremic toxins can induce cardiovascular diseases including ischemic heart disease, congestive heart failure, arrhythmias, and peripheral vascular disease via several

mechanisms. Firstly, uremic toxins can trigger atherosclerosis, which is the primary cause of CVD by induction of adipocyte and cholesterol transport dysfunction and increased oxidative stress and inflammatory cytokines production[12, 13]. Some uremic toxins also promote endothelial injury, platelet aggregation, and thrombus formation[14]. Furthermore, they can enhance the transformation of vascular smooth muscle cells (VSMCs) into osteoblastic-like cells, leading to vascular calcification progression[15].

Besides the vascular system, uremic toxins also have direct and indirect effects on cardiomyocytes. The oxidative stress and inflammation promoted by uremic toxins can enhance the progression of cardiac hypertrophy and cardiac fibrosis. Meanwhile, uremic toxins are taken up by cardiomyocytes and subsequently activate the nuclear factor kappa B (NF-**K**B) pathways, resulting in the promotion of cardiac remodeling and fibrotic change[16]. Figure. 3 depicts the pathophysiology of uremic toxin-associated CVD.

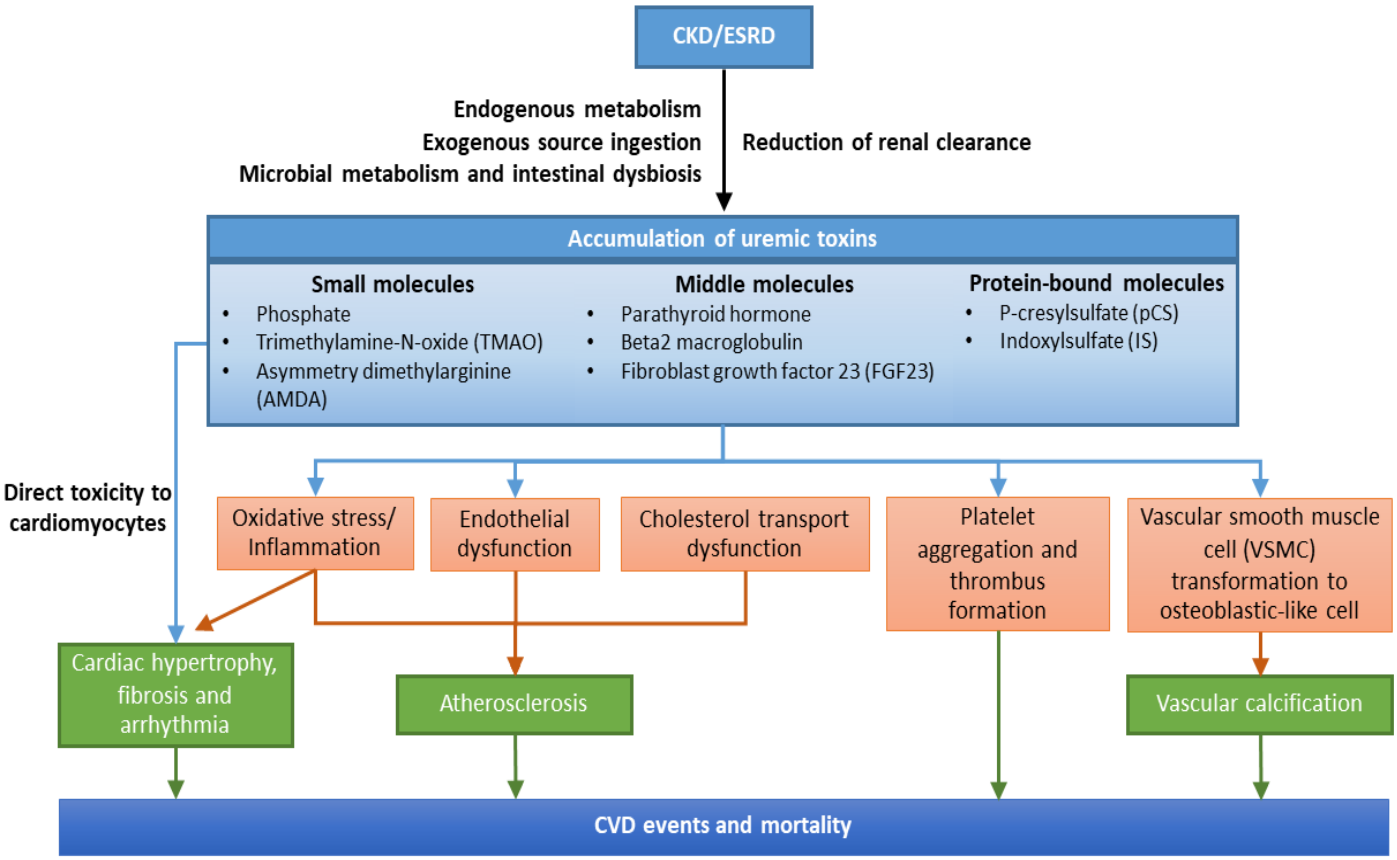

Figure 3 Pathophysiology of uremic toxins-associated cardiovascular disease

Protein-bound uremic toxins

Most compounds in this group have low molecular weight and high albumin binding affinity. Therefore, it is difficult to remove these toxins by conventional hemodialysis. Several studies have demonstrated that protein-bound uremic toxins, especially p-cresyl sulfate and indoxyl sulfate, are strongly associated with cardiovascular disease and poor prognosis in CKD and dialysis patients.

P-cresyl sulfate

P-cresyl sulfate is one of the established important protein-bound uremic toxins. It is a by-product of the intestinal bacterial metabolism of protein diet. P-cresyl sulfate is generated from p-cresol which is produced from the breakdown of phenylalanine and

tyrosine by anaerobic micro-organism and is absorbed into the circulation. In the liver, conjugation of p-cresol through glucuronidation and sulfation creates p-cresyl sulfate and p-cresyl glucuronide, respectively. Elevation of serum p-cresyl sulfate level results from decreased renal excretion and change in the intestinal microbiome, which promotes the production of these compounds[17]. A previous observational study reported the relationship between serum levels of p-cresyl sulfate and renal function in CKD patients. The mean serum p-cresyl sulfate levels were 4.87±4.3, 5.97±5.6, and 12.47±7.9 mg/L in patients with stage 3, 4, and 5 CKD, respectively[18].

p-cresyl sulfate is also known as a vascular toxin since it induces inflammation and oxidative stress by leukocyte activation causing vascular endothelial injury and reduction of nitric oxide production[19, 20]. According to a previous systematic review of in vitro and in vivo 27 studies, there were positive correlations between serum p-cresyl sulfate level and vascular dysfunction and aortic calcification[21]. Furthermore, according to a recent meta-analysis, serum p-cresyl sulfate level was significantly associated with cardiovascular events and all-cause mortality in CKD patients[4].

Indoxyl sulfate

Indoxyl sulfate is an important protein-bound uremic toxin derived from indole, a by-product of tryptophan metabolism of the gut microbiome. Indole is metabolized and transformed to indoxyl sulfate in the liver. In similar to p-cresyl sulfate, the accumulation of indoxyl sulfate in CKD patients is due to reduced renal function and dysbiosis of intestinal microbiota[22]. Serum indoxyl sulfate level increased gradually as renal function declined and reached a peak at the CKD stage 5. The mean serum indoxyl sulfate levels were 3.27±3.0, 5.47±3.6, 19.97±10.5 mg/L in patients with stages 3, 4, and 5 CKD, respectively[18].

Indoxyl sulfate is considered as an atherosclerosis accelerator by increasing proinflammatory cytokines and oxidative stress, promoting endothelial dysfunction, inhibiting bone turnover, and inducing vascular calcification[23]. Moreover, indoxyl sulfate contributes to cardiac fibrosis through transforming growth factor-beta synthesis and

alpha collagen. Liu et al. found that indoxyl sulfate encouraged the subsequent activation of the NF-kB pathway, leading to the expressions of cardiac hypertrophy and cardiac fibrosis[24]. Barreto et al. performed a prospective cohort study and demonstrated that serum indoxyl sulfate significantly impacted vascular diseases and higher mortality in CKD patients[25].

Protein-bound uremic toxins lowering methods

Several treatment modalities have been performed to seek the most effective strategies in lowering serum p-cresyl sulfate and indoxyl sulfate levels. The rationales of the treatment modalities to decrease protein-bound uremic toxins are based on the mechanisms of production and elimination of these uremic toxins. Since p-cresyl sulfate and indoxyl sulfate are derived from colonic microbial metabolic products using dietary amino acids as the substrates, the colon has become a potential target for treatment to reduce the toxicity caused by gut-derived protein-bound uremic toxins. Attenuating the production of gut-derived protein-bound uremic toxins in pre-dialysis CKD can be divided into three main strategies: dietary protein restriction, maintenance of gut homeostasis by biotic supplements, and oral sorbents.

1. Dietary protein restriction

p-cresyl sulfate and indoxyl sulfate result from bacterial metabolism of protein in the colon. Therefore, dietary protein restriction might be an effective therapeutic strategy that reduces the substrate of these toxins. Pre-dialysis CKD patients are basically recommended to restrict daily protein intake of about 0.6-0.8 g/kg/day or, as recommended by the current recommendation, a very low protein diet (VLPD; 0.3-0.5 g/kg/day) combined with ketoanalogue (KA)[26]. There were no available controlled studies or RCTs regarding this issue. In cross-sectional and cohort studies, one study showed a significant effect of VLPD (0.3 g/kg/day) plus KA on p-cresyl sulfate reduction compared with a low protein diet (0.6 g/kg/day)[27]. Marzocco et al. reported in non-dialysis CKD patients that VLPD (0.3 g/kg/day) supplemented with ketoanalogues significantly decreased serum

indoxyl sulfate levels with a reduction of 36% when compared with a low protein diet (0.6 g/kg/day) ($p < 0.001$)[28]. In comparison, a study in pre-dialysis CKD patients by Black et al. showed that 6-month treatment with low protein diet yielded no significant change of serum indoxyl sulfate levels[29]. Therefore, the lowering effect of dietary protein restriction on protein-bound uremic toxins is still controversial. In addition, there was a significant concern about malnutrition in CKD patients who restrict VLPD.

2. Maintenance of gut homeostasis by biotic supplements

The aim of supplementing biotics, including prebiotics (nondigestible dietary fiber such as inulin and fructo-oligosaccharides) , probiotics (supplementation of a specific combination of bacteria), or synbiotics (co-administration of pre- and probiotics), is to attenuate dysbiosis by providing appreciable changes of the microbiome (enrichment of saccharolytic bacteria and depletion of proteolytic bacteria). The common substances utilized as prebiotics include lactulose, oligofructose-enriched inulin, galacto-oligosaccharide, and acarbose while the usual bacteria used as probiotics comprise *Lactobacillus* spp and *Bifidobacterium* spp[30].

Several studies investigated the p-cresyl sulfate and indoxyl sulfate lowering effect of pre-biotics. An observational study by Meijers et al. reported that 4-week of dietary fiber prebiotic oligofructose-inulin significantly reduced p-cresyl sulfate generation rates and decreased serum concentrations. In contrast, neither indoxyl sulfate generation rates nor serum concentrations were significantly changed[31]. Three recent randomized controlled trials by Sirich et al., Esgalhado et al., and Khosroshahi et al. showed conflicting results[32-34]. Probiotic supplements failed to reduce protein-bound uremic toxins in recent RCTs[35].

3. Oral sorbents

Administration of oral adsorbent could potentially reduce precursors of protein-bound uremic toxins by absorbing and enhancing fecal excretion of protein-bound uremic toxins substrate. AST-120, a synthesized carbon adsorbent, is one of the most widely studied oral adsorbents. It is presumed to bind indole in the colon, prevent its absorption and decrease its eventual conversion to indoxyl sulfate[36]. In this regard, the effect of AST-120 on protein-bound uremic toxins reduction, mostly focusing on indoxyl sulfate, has been studied for several years. According to observational and randomized controlled studies, AST-120 seems to exert a beneficial effect on indoxyl sulfate reduction[37-39]. However, the evidence on the benefits of AST-120 on p-cresyl sulfate is still limited.

Takkavatakarn et al. conducted a systematic review and meta-analysis to comprehensively evaluate the effectiveness of current protein-bound uremic toxins lowering strategies. The results showed that prebiotic and synbiotic supplements could effectively reduce p-cresyl sulfate and indoxyl sulfate levels in CKD patients compared with placebo, while probiotics had no beneficial effects on protein-bound uremic toxins reduction. However, there was tremendous heterogeneity in the population, biotic strains, and probiotic formulation[40] (Table 3). The effect of biotic supplements was detected only in dialysis patients. In addition, there were a significant decrease in serum indoxyl sulfate levels in patients treated with AST-120, oral charcoal adsorbent, compared with placebo. Although the results were limited due to the small number of studies and most studies limited in sample size, the results suggested the potential benefit of oral absorbent in the reduction of gut-derived, protein-bound uremic toxins.

Table 3 Summary protein-bound uremic toxins reduction according to treatment modality in controlled studies and randomized controlled trials

Novel strategies	No of studies	No of patients	Weight mean net difference	p-value	I^2 index	p-value	Egger's test p-value
Indoxyl sulfate							
Biotics	11	498	-4.24 (-6.56, -1.92)	<0.001	86.88	<0.001	0.039
: Pre-biotics	3	115	-4.66 (-7.04, -2.29)	<0.001	48.609	0.143	-
: Pro-biotics	3	71	-3.93 (-11.84, 3.98)	0.331	86.435	0.001	-
: Synbiotics	5	312	-4.87 (-7.99, -1.75)	0.002	67.866	0.014	-
AST-120	4	785	-7.73 (-12.17,-3.27)	0.001	91.135	<0.001	0.34
Dialysis techniques	8	414	1.56 (-4.74, 7.86)	0.627	98.041	<0.001	0.438
: Hemodiafiltration	5	240	0.25 (-2.70, 3.19)	0.87	84.228	<0.001	-
: Citrate dialysate	2	152	7.30 (-12.59, 27.19)	0.472	96.013	<0.001	-
Residual renal function	3	369	-5.83 (-9.72, -1.94)	0.003	93.243	<0.001	0.727
P-cresyl sulfate							
Biotics	8	272	-1.99 (-4.15, 0.16)	0.069	66.866	0.004	0.721
: Pre-biotics	3	115	-3.312 (-4.800, -1.825)	<0.001	0	0.534	-
: Pro-biotics	2	49	2.421 (-6.521, 11.362)	0.596	51.218	0.152	-
: Synbiotics	3	108	-3.741 (-7.158, -0.323)	0.032	34.146	0.219	-
AST-120	2	170	-8.97 (-12.83, -5.11)	<0.001	0	0.57	NA
Dialysis techniques	4	136	-3.582 (-4.631, -2.533)	<0.001	0	0.724	0.699
: Hemodiafiltration	3	114	-3.714 (-4.802, -2.627)	<0.001	0	0.778	-

Chronic kidney disease-mineral and bone disorder (CKD-MBD)

Chronic kidney disease–mineral and bone disorder (CKD-MBD) is a term defined in 2005 by Kidney Disease: Improving Global Outcomes (KDIGO) to highlight that disorders of calcium, phosphorus, parathyroid hormone (PTH), and fibroblast growth factor 23 (FGF23) in CKD patients. These mineral and hormone alterations may lead to derangement in bone metabolism (renal osteodystrophy), vascular calcification, and cardiovascular death. The pathophysiology of CKD-MBD is a complex process. Figure 4 illustrates the pathogenesis of mineral bone disorders in CKD.

Hyperphosphatemia

As renal function declines, phosphate excretion is increased by reducing the tubular reabsorption of filtered phosphate in the remaining nephrons under the influence of FGF23 and PTH to maintain normal serum phosphate levels. In stage 4-5 CKD, the adaptation is no longer adequate, and hyperphosphatemia develops despite high FGF23 levels[41]. Hyperphosphatemia exerts other important effects in the CKD-MBD axis, especially in the parathyroid gland. Hyperphosphatemia directly stimulates PTH production and produces nodular hyperplasia in the parathyroid gland[42]. Hyperphosphatemia also stimulates osteoblastic transition in the vasculature and directly contributes to extraskeletal mineralization through an elevated calcium-phosphorus product[43].

Hyperparathyroidism

As CKD progresses, the parathyroid glands are continuously stimulated by a combination of hyperphosphatemia, decreased calcium concentration, and markedly reduced serum calcitriol leading to increased PTH synthesis and release. At the same time, elevated FGF-23 expression downregulates residual renal 25(OH)-1-hydroxylase, which exacerbates the deficiency of calcitriol, acting as an additional driver to nodular hyperplasia and secondary hyperparathyroidism[44]. Nodular transformation in advanced

secondary hyperparathyroidism is accompanied by a reduction in vitamin D receptor (VDR) and calcium sensing receptor (CaSR) expression and decreased sensitivity to the inhibitory effect of calcium and calcitriol on PTH secretion[45]. This excess PTH leads to mobilization of calcium from the bone. The outcome is a high turnover renal osteodystrophy, excess bone resorption, skeletal frailty and elevated fracture risk[46].

Klotho

Klotho is a transmembrane protein that confers tissue specificity to FGF23 and highly expressed in very few tissues including the proximal and distal renal tubules and parathyroid glands. Klotho expression is significantly reduced in CKD. The klotho deficiency results in loss of negative feedback to FGF23 secretion and the continual production of FGF23 and secretion by the osteocyte[47].

Fibroblast growth factor 23 (FGF23)

FGF23, a 32,000 Dalton peptide hormone, is mainly generated by osteocytes and plays a principal role in the complex interrelationship between bones and other tissues. FGF23 production is stimulated by several factors including phosphate, calcium, PTH, 1,25-dihydroxyvitamin D [1,25(OH)2D][48]. At tissue level, FGF23 acts by combining with various FGF receptors (FGFR) in either α-Klotho, a FGF23 co-receptor, dependent fashion, as occurring in the kidney and parathyroid gland[49], or α-Klotho independent manner, as developing in the heart, liver, immune system, skeleton, and bone marrow. Under normal physiology, the main functions of FGF23 are to enhance phosphaturia, decrease calcitriol synthesis, and reduce PTH generation[50]. Circulating FGF23 starts to elevate in the early stage of CKD before the development of other abnormalities. High levels of FGF23 attenuate hyperphosphatemia at the expense of 1,25(OH)2 vitamin D suppression, thus initiating the development of secondary hyperparathyroidism.[51].

Indeed, FGF23 level continuously rises during progression of CKD. In late CKD, the very high levels of FGF23 permit anomalous FGF receptor activation independent of Klotho and result in unique FGF23-stimulated pathologies. Several experimental and

epidemiological studies in CKD illustrated correlations between high FGF23 levels and various deleterious effects on the aforementioned tissues, including left ventricular hypertrophy (LVH)[52], vascular calcification[53], impaired immune system, anemia, and decreased bone mineralization[54].

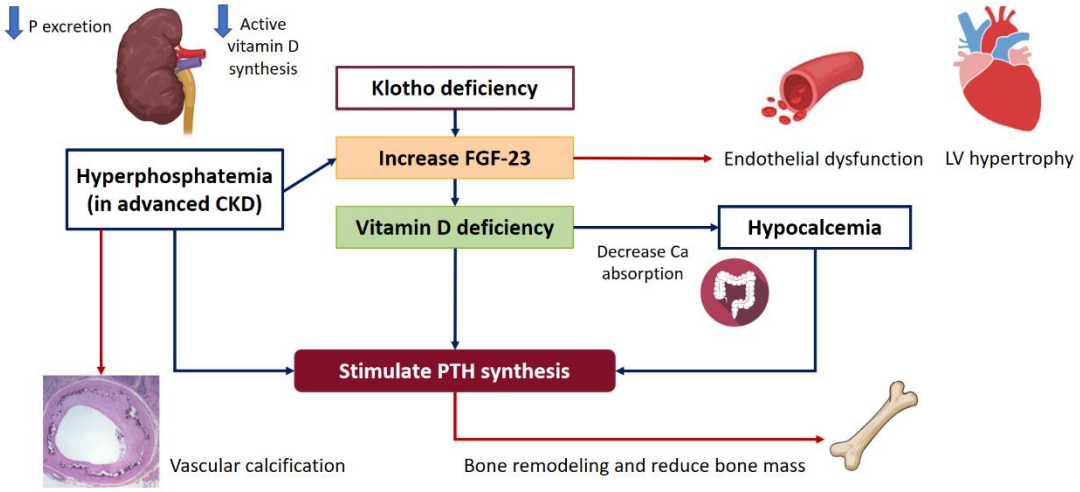

Figure 4 Pathogenesis of disordered mineral bone metabolism in CKD

Numerous attempts have been performed to lower FGF23 level in CKD patients. Several studies investigated the modalities to reduce FGF23 according to the stimulating factors, including dietary phosphate restriction, phosphate binders, iron supplements, calcimimetics, and parathyroidectomy. With respect to enhancing FGF23 removal in dialysis patients, the roles of hemodialysis, hemodiafiltration (HDF), adsorption techniques, and preservation of residual renal function (RRF) on FGF23 level have also been examined. Takkavatakarn et al. performed the systematic review and meta-analysis to synthesize the data on the effectiveness of FGF23 lowering strategies in CKD patients. The results showed that non-calcium-based and iron-based phosphate binders, iron supplements, calcimimetics, hemoperfusion, and preservation of RRF could effectively reduce FGF23 in CKD patients[55]. Interestingly, in non-dialysis CKD patients, only sevelamer could significantly reduce FGF23 levels (Figure 5). No trend of reduction in

FGF23 levels was identified in patients receiving lanthanum, another non-calcium-based phosphate binder (Figure 6).

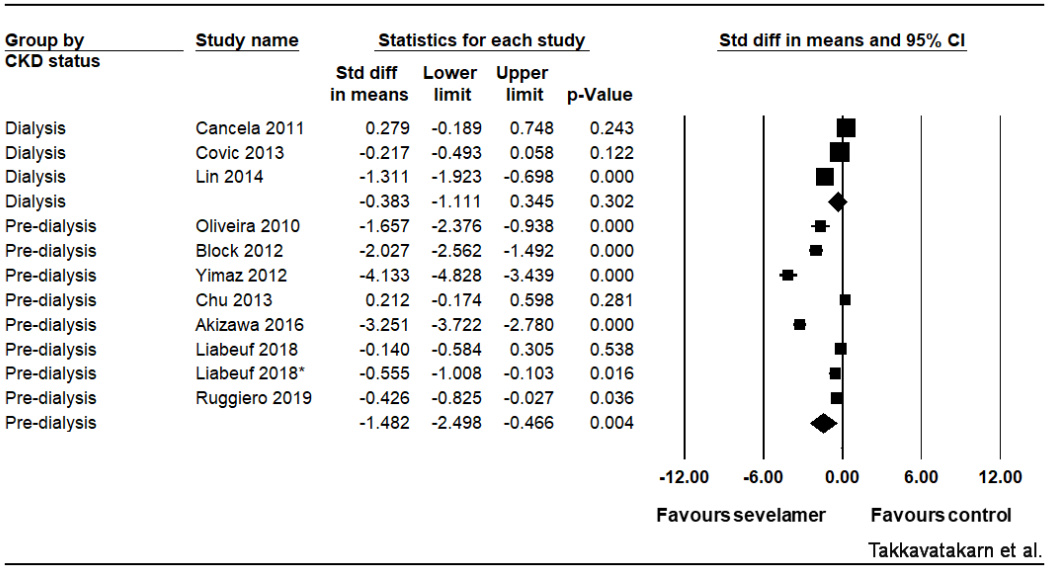

Figure 5 Forest plot for fibroblast growth factor 23 lowering effect of sevelamer in dialysis and pre-dialysis chronic kidney disease patients

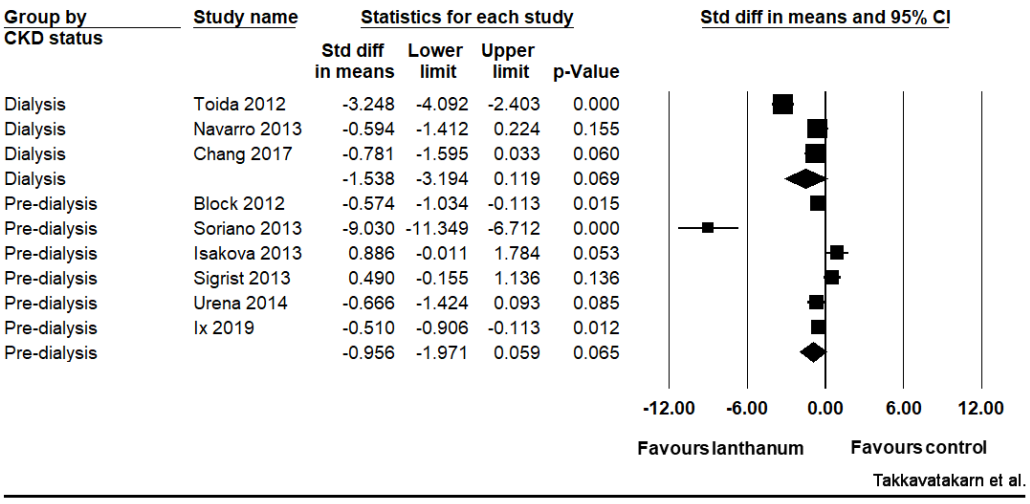

Figure 6 Forest plot for fibroblast growth factor 23 lowering effect of lanthanum in dialysis and pre-dialysis chronic kidney disease patients

Sevelamer

Sevelamer is an orally administered non-absorbed anion exchange resin commonly used as a phosphate binder in CKD patients with hyperphosphatemia. Sevelamer composition contains multiple amines, separated by one carbon in the polymer backbone, which is partially ionized in the intestine and interacts with phosphorus through hydrogen and ionic bonds. Therefore, concomitant administration with food, sevelamer could capture dietary phosphorus in the gastrointestinal tract, reduce intestinal absorption, and lessen serum phosphate concentration[56].

Besides lowering phosphate levels, several studies revealed that sevelamer provided pleiotropic effects on the cardiovascular system. Sevelamer significantly reduced serum levels of total cholesterol, low-density lipoprotein cholesterol, and advanced glycation endproducts (AGEs) compared with calcium carbonate in CKD patients. In addition, previous studies also reported the effects of sevelamer on endotoxins reduction[57, 58]. Theoretically, the pleiotropic effect of sevelamer has been associated with the reduction of vascular calcification, inflammation, cardiovascular events, mortality in CKD patients. A recent meta-analysis of randomized controlled trials compared sevelamer and calcium-based binders for hyperphosphatemia treatment reported significantly decreased fibroblast growth factor-23 (FGF23), coronary artery calcification, and all-cause mortality[59].

As sevelamer is not absorbed in the gastrointestinal tract, sevelamer effectively binds with bile salts and captures other molecules in the intestinal lumen, resulting in the reduction of these substance absorptions. The human gastrointestinal tract contains > 100 trillion bacteria that participate in various activities, including degradation of indigestible substances, production of vitamins and fatty acid, maintenance of tight junction of the intestinal epithelium, and the development of the immune system[60]. Moreover, the gastrointestinal tract is a substantial source of uremic toxins[61]. In CKD patients, the high concentration of urea in gastric secretion, diet restriction, multiple drug uses resulted in the alteration of the gut microbiome from the healthy state. The microbiota dysbiosis promotes systemic inflammation and uremic toxin production, and breakdown

of the gut epithelial barrier. The expansion of bacterial families which produce p-cresol and indole (p-cresyl sulfate and indoxyl sulfate substances) was observed in CKD patients compared with healthy participants[62].

The application of sevelamer as the intestinal molecule absorbent has been studied for several years. p-cresyl sulfate and indoxyl sulfate are some of the most widely examined gut-derived uremic toxins. A prospective cohort in 5 hemodialysis patients reported a significant reduction of serum p-cresyl sulfate from 31.3±10.06 mg/L to 19.70±10.5 mg/L after treatment with 2.4 gram per day of sevelamer for 12 weeks[63]. Previous in vitro, in vivo, and observational clinical studies exploring the effect of sevelamer on p-cresyl sulfate were summarized in Table 4. Two recent randomized controlled trials reported conflicting results. Riccio et al. showed that sevelamer carbonate effectively reduced serum p-cresyl sulfate in pre-dialysis CKD patients compared with placebo after 12 weeks of treatment[64]. In comparison, Bennis et al. reported the insignificant association between a 12- week of treatment with sevelamer carbonate and serum p-cresyl sulfate changes in CKD 3b and 4[65]. The different results might be explained by the different populations, baseline renal function, and doses of the treatment doses.

With regard to serum indoxyl sulfate reduction, an *in vitro* study showed that sevelamer hydrochloride binds indole 10–15%[66]. However, in a previous observational study in 5 hemodialysis patients, sevelamer did not reduce serum indoxyl sulfate levels after 12 weeks[63] (Table 4). In addition, a previous *post hoc* study showed that serum indoxyl sulfate did not alter in patients receiving sevelamer for 12 weeks.

Our study aims to investigate the effect of sevelamer as an oral adsorbent compared with calcium-based phosphate binder in pre-dialysis CKD patients with hyperphosphatemia. The primary outcome is the change of serum p-cresyl sulfate levels after 24 weeks of treatment. The secondary outcomes are the change of serum indoxyl sulfate, high sensitivity C reactive protein levels, estimated glomerular filtration rate after 24 weeks of treatment, cardiovascular event, dialysis initiation, and adverse events

Table 4 *In vitro*, *in vitro*, and observational clinical studies exploring the effects of sevelamer on p-stylcresyl sulfate and indoxyl sulfate

Author	Year	Type of study	Sample	Parameters	Results
DeSmet et al[66]	2003	*In vitro*	N/A	P-cresol, indole	Sevelamer was able to adsorb indole (10-15%) and p-cresol (40-50%).
Phan et al[67]	2005	*In vivo*	Apolipoprotein E–deficient mouse (uremic and non-uremic mice)	Atherosclerosis and vascular calcification, Indole	No change in serum indole in response to sevelamer treatment
Guida et al[68]	2013	Cross-sectional study	Fifty-seven peritoneal dialysis patients	p-cresol	Significant lower p-cresol in patients treated sevelamer than other phosphate binders
Lin et al[63]	2017	Prospective cohort	Five hemodialysis patients	p-cresyl sulfate, in/doxyl sulfate	Significant reduction of serum p-cresyl sulfate levels but no effect on indoxyl sulfate

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CHAPTER III
MATERIALS AND METHODS

Population and Sample

- **Target population** Thai pre-dialysis chronic kidney disease patients with hyperphosphatemia

- **Study population** Thai pre-dialysis chronic kidney disease patients with hyperphosphatemia in King Chulalongkorn Memorial Hospital

- **Sample size**

Sample size was calculated using total p-cresol as the main variable and assuming a power of 80% and a two-sided alpha of 5%.

According to previous study of Riccio et al[64]. the mean serum p-cresyl sulfate of sevelamer and treatment groups were 3.44±2.45 mg/L and 7.33±5.28 mg/L, respectively.

α = 0.05; $Z_{\alpha/2}$= 1.960

β = 0.2 (power 80%); $Z\beta$ = 0.842

Δ = 3.89;

r = 1

$$n_{trt} = \frac{(z_{1-\frac{\alpha}{2}} + z_{1-\beta})^2 \left[\sigma_{trt}^2 + \frac{\sigma_{con}^2}{r}\right]}{\Delta^2}$$

$$r = \frac{n_{con}}{n_{trt}}, \Delta = \mu_{trt} - \mu_{con}$$

$$n = \frac{(1.959 + 0.841)^2 \times (2.45^2 + 5.28^2/1)}{(3.89)^2} = 17.55$$

n = 18 for each group

Total enrolled cases = 36 cases

Considering a drop-out rate of 10% total sample size required is 40 patients

Inclusion criteria

Patients must meet all inclusion criteria as follows:

1. Patients age 18 years old or older.
2. Non-dialysis patients who have eGFR < 60 ml/min/1.73m^2 (defined by CKD-EPI equation) at least 3 months
3. Hyperphosphatemia (> 5.0 mg/dL)

Exclusion criteria

1. Existing or previous treatment with any phosphate binder within the last 1 month
2. Recently adjust doses of vitamin D analog within 3 months
3. Patients with serum calcium more than 10.2 mg/dL
4. Known pregnancy
5. History of renal allograft

Operational definition

1. **Chronic kidney disease (CKD)**

   Patients with estimated glomerular filtration rate (eGFR) less than 60 ml/min/1.73 m2 for more than three months.

2. **End-stage renal disease (ESRD)**

   ESRD is defined as the need for maintenance dialysis (peritoneal or hemodialysis) for at least 28 days.

3. **Cardiovascular events**

Cardiovascular events are defined as myocardial infarction, unstable angina, nonfatal heart failure, ischemic stroke, and peripheral artery disease.

Observational and Measurement

1. **Independent variable:** Oral phosphate binders (Sevelamer or Calcium carbonate)
2. **Dependent variables:** Serum levels of p-cresyl sulfate, indoxyl sulfate, high sensitivity C reactive protein, phosphate, calcium, parathyroid hormone, FGF23, creatinine, and eGFR at baseline, 12, and 24 weeks, cardiovascular events, time to ESRD, and mortality.

Study Methodology

Screening

At the outpatient unit of King Chulalongkorn Memorial hospital, investigators provided research information including methodology, risk, and benefit of this study, to all potential participants and caregivers in both oral and written forms. All of the potential patients' questions were answered by investigators. The participants had freedom in deciding whether to participate in the study or not. The participants who decided to participate in this study had to sign the consent form before starting the research protocol.

Run-in period

All participants were given dietary advice for CKD, including low protein (0.6-0.8 g/kg/day), low salt (< 5 g NaCl per day), and low phosphate diet (< 800 mg per day) from dietitians. After two weeks of the run-in period, patients who had persistent hyperphosphatemia (> 5 mg/dL) were randomly assigned to receive either sevelamer or calcium carbonate.

Randomization

The randomization sequence was obtained using a randomly generated list in the block of six. The enrolled participants were randomly assigned (1:1) by block

randomization to receive 2,400 mg of sevelamer (3 tablets per day) or 1,500 mg of calcium carbonate (1.5 tablets per day). Drug dosage was adjusted according to serum phosphate level.

Interventions

- This study used sevelamer carbonate (Renvela®) 800 mg per tablet or calcium carbonate 1,000 mg per tablet (containing calcium element for 400 mg per tablet.)
- All patients received 6 months of treatment with 2,400 mg of sevelamer (3 tablets per day) or 1,500 mg of calcium carbonate (1.5 tablets per day).
- Drug dosage was adjusted according to phosphate level after 3 months of treatment. Dosage was reduced 50% in patients who had hypophosphatemia (< 2.5 mg/dL) and serum phosphate was collected in the next 4 weeks after dose adjustment.
- Compliance to medication was assessed using pill counts.
- Concomitant pharmacological and non-pharmacological therapies such as renin-angiotensin-aldosterone blockage, anemia management, and blood pressure control were prescribed to all patients according to the therapeutic target of standard guidelines.
- Patients were advised to restrict protein diet 0.6-0.8 g/kg/day and re-checked the restriction by physician and dietitian throughout the study period.
- Withdrawal from the study was considered in case of drug intolerance, persistent hypophosphatemia (< 2.5 mg/dL) or hypercalcemia (> 10.2 mg/dL) on two sequential blood tests after dose adjustment, or participants indicated to initiate renal replacement therapy.

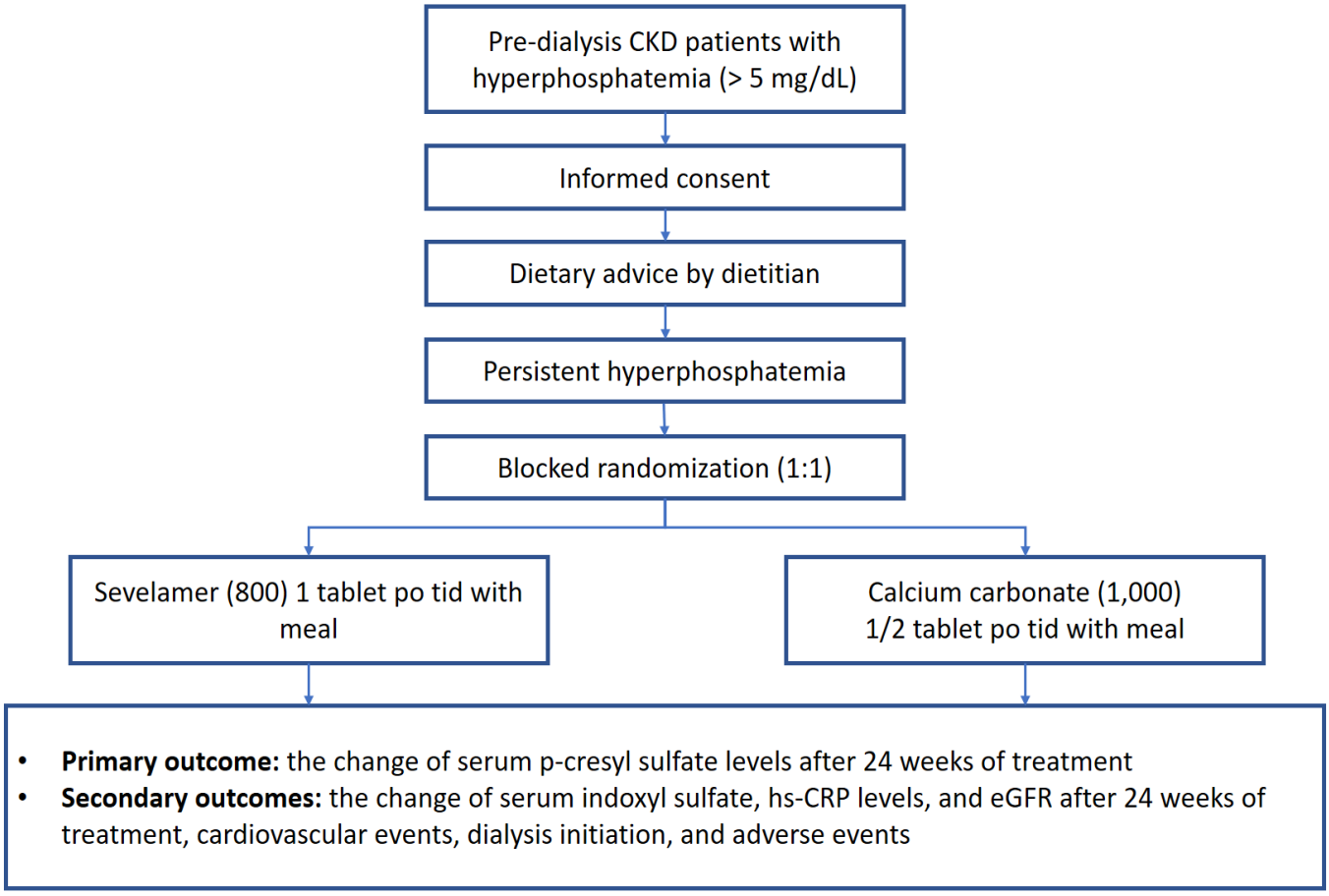

Figure 7 Study flow

Data collection (Table 5)

Demographic data, including age, sex, causes of CKD, and medical history, were obtained. A blinded cardiologist performed cardio-ankle vascular index (CAVI) and echocardiography at baseline.

At each time of the study (baseline, 6, 12, and 24 weeks), a complete clinical evaluation, including body weight and blood pressure measurement, was performed. The biochemical parameters were obtained. Urinary urea nitrogen, creatinine, sodium, phosphate, and protein excretion were measured in 24-hour urine. Dietary protein intake (DPI) was estimated by daily urinary excretion of urea nitrogen. Renal function was expressed as estimated glomerular filtration rate (eGFR) which was calculated by CKD-EPI equation.

Serum p-cresyl sulfate, indoxyl sulfate, fibroblast growth factor 23 (FGF23), intact parathyroid hormone (iPTH), lipid profile, and high sensitivity-C reactive protein (hs-CRP) were measured at baseline, 12, and 24 weeks. The serum level of p-cresyl sulfate was determined by high-performance liquid chromatography (HPLC) at the Pharmacology Department, Faculty of Medicine, Chulalongkorn University. The average intra-assay coefficient of variation (CV) of HPLC was 1.65%. The laboratory technician was blinded to the treatment assignment. The PTH levels were measured using a chemiluminescence immunoassay on a Roche Elecsys 2010 Analyzer. This assay detected both intact PTH and a fragment containing amino acids 7 to 84. The FGF23 levels were assessed using a Human intact FGF23 ELISA kit (Millipore Corporation, Billerica, MA, United States). The lowest detection limit was 3.5 pg/mL with an Intra-assay and inter-assay coefficient of less than 10% variations.

Ankle-brachial Index (ABI) and cardio-ankle vascular index (CAVI) were used to determine the vascular complications using a portable ultrasonography-based machine (VaSera VS-200; Fukuda-Denshi Company, Tokyo, Japan). ABI is calculated by the highest systolic pressure on foot of that side/ average of the highest pressure from both arms, while CAVI score was calculated by the machine. The ABI score < 0.9 and 0.91-0.99 are peripheral arterial disease and borderline, respectively, while ABI at 1-1.4 and >1.4 are normal and non-compressible arteries[69]. The CAVI score < 8 and 8-9 are normal and at risk for atherosclerosis, while CAVI > 9 is possible atherosclerosis[70].

Table 5 Data Collection

	Screening	Baseline	6 weeks	12 weeks	24 weeks
Inclusion and Exclusion criteria	✓				
Demographic data	✓				
Cause of chronic kidney disease	✓				
Underlying disease	✓				
Laboratory data	✓	✓	✓	✓	✓
24-hour urine	✓	✓	✓	✓	✓
p-cresyl sulfate		✓		✓	✓
Indoxyl sulfate		✓		✓	✓
Fibroblast growth factor 23		✓		✓	✓
High sensitivity C reactive protein		✓		✓	✓
Lipid profiles		✓		✓	✓
Parathyroid hormone		✓		✓	✓
Cardio-ankle vascular index		✓			✓
Echocardiography		✓			
Renal replacement therapy status		✓	✓	✓	✓
Cardiovascular events		✓	✓	✓	✓
Dead or alive status		✓	✓	✓	✓
Adverse events		✓	✓	✓	✓

Data analysis

All analyses adhered to the intention-to-treat principle. We described patient characteristics using mean ± (standard deviation; SD) for normally distributed or median (interquartile range; IQR) for non-normally distributed continuous variables. Categorical data were described as numbers and percentages. We compared patients' characteristics using chi-square, unpaired t tests, and Mann-Whitney U test as appropriate.

The changes in primary and secondary outcomes from baseline in each group were compared using a paired t test. Treatment effects on variables among patients treated with sevelamer or calcium carbonate, were examined using linear mixed-effects models for repeated measures over time, including data of the baseline, 12th week and 24th week. A random intercept model was used with time coded as categorical factor. Difference between the groups were estimated by including in the model the interaction term between visit and treatment. Correlation between variables was determined by linear regression analysis. Results were reported as estimated marginal mean with 95% confidence intervals (95% CI). A two-tailed p-value < 0.05 was considered significant. Data were analyzed using Stata version 15.

CHAPTER IV
RESULTS

Patients Characteristics

Among 250 pre-dialysis CKD patients at the outpatient department of King Chulalongkorn Memorial Hospital, 48 patients were eligible for inclusion in this trial. Forty patients with persistent hyperphosphatemia after the run-in period were randomized to receive sevelamer (n = 20) or calcium carbonate (n = 20) (Figure 8). At randomization, the mean serum phosphate was 5.50 ± 0.78 and 5.39 ± 0.44 mg/dL in sevelamer and calcium carbonate groups, respectively. Most of the patients were CKD stage 5 (90%). Diabetic nephropathy was the most common cause of CKD in both groups. There were no differences between the two groups at baseline in demographic data, renal function, laboratory parameters, CAVI, left ventricular mass index (LVMI), and left ventricular ejection fraction (LVEF). Fifty-five percent of patients had CAVI > 8. More than 80 percent of the patients in both groups were diagnosed left ventricular hypertrophy. Serum p-cresyl sulfate levels were 10.75 ± 9.84 and 8.75 ± 5.36 mg/L in sevelamer and calcium carbonate groups, respectively (Table 6).

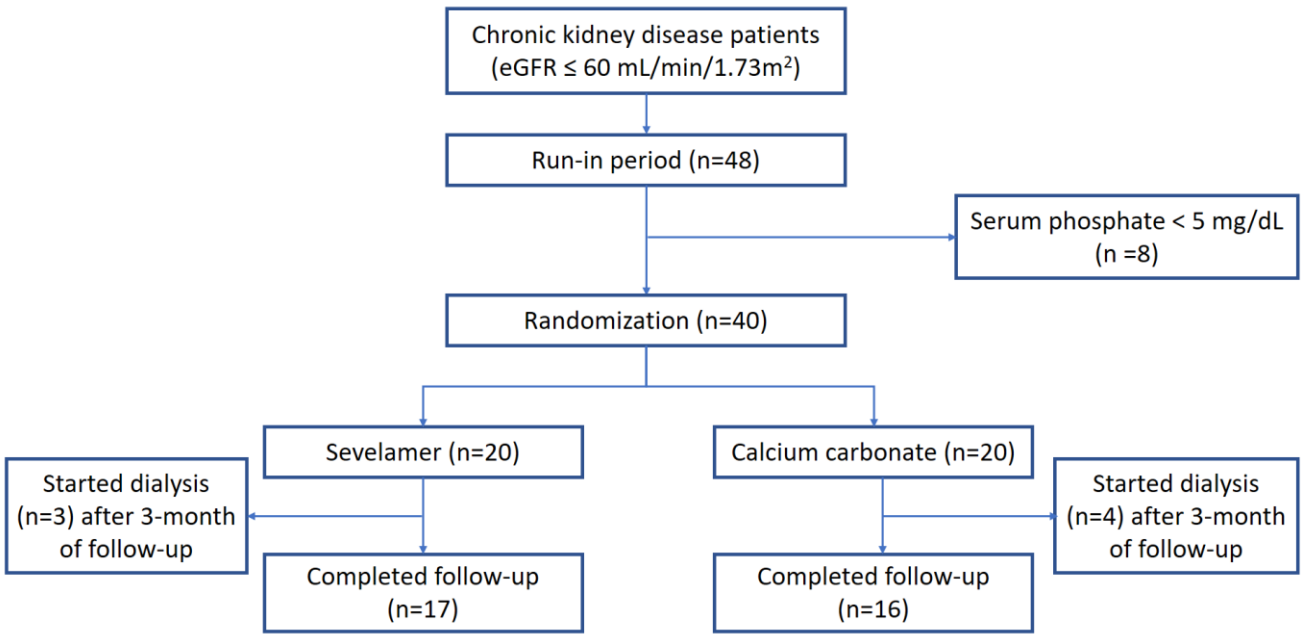

Figure 8 Flow chart of patient allocation

Table 6 Baseline demographic, biochemical, and clinical data between sevelamer and calcium carbonate groups.

Parameters	Sevelamer (n=20)	Calcium carbonate (n=20)
Age (years)	59.8 ± 13.23	52.05 ± 16.39
BMI (kg/m^2)	26.08 ± 5.27	26.94 ± 5.97
Cause of CKD (%)		
Diabetic nephropathy	12 (60%)	8 (40%)
Hypertensive nephropathy	1 (5%)	4 (20%)
Chronic glomerulonephritis	1 (5%)	2 (10%)
ADPKD	1 (5%)	1 (5%)
Unknown	5 (25%)	5 (25%)
BUN (mg/dL)	69.1 ± 16.37	68.43 ± 19.5
Creatinine (mg/dL)	6.51 ± 3.07	6.03 ± 2.61
eGFR (mL/min/1.73m^2)	9.79 ± 6.72	11.08 ± 8.86
CKD stage		
4 (eGFR 15-30 mL/min/1.73m^2)	3 (15%)	1 (5%)
5 (eGFR < 15 mL/min/1.73m^2)	17 (85%)	19 (95%)
Hemoglobin (g/dL)	9.76 ± 1.07	9.44 ± 1.14
Calcium (mg/dL)	8.96 ± 0.8	8.88 ± 1.45
Phosphate (mg/dL)	5.50 ± 0.78	5.39 ± 0.44
Albumin (g/dL)	3.94 ± 0.44	3.87 ± 0.35
LDL cholesterol (mg/dL)	112.89 ± 57.48	89 ± 31.81
HDL cholesterol (mg/dL)	40.97 ± 14.5	42.68 ± 13.56
25 OH vitamin D (ng/mL)	25.85 ± 11.37	26.68 ± 17.41
iPTH (pg/mL)	336.5 ± 184.05	303.78 ± 225.71
Hs-CRP (mg/L)	0.81 (0.96)	0.8 (2.75)
FGF23 (pg/mL)	47.19 (91.08)	61.50 (83.73)
Urine sodium (g/day)	136.13 ± 43.63	167.02 ± 82.42

Proteinuria (g/day)	2.12 ± 1.58	2.45 ±1.74
Dietary protein intake (g/kg/day)	0.55 ± 0.24	0.56 ± 0.19
ABI	1.1 ± 0.10	1.09 ± 0.94
CAVI	8.36 ± 1.12	7.47 ±1.28
LVEF (%)	62.48 ± 14.89	65.52 ± 7.8
LVMI (g/m^2)	123.19 ± 38.5	124.24 ± 35.27
LVH (%)	17 (85%)	16 (80%)
Serum p-cresyl sulfate (mg/L)	10.75 ± 9.84	8.75 ± 5.36
Serum indoxyl sulfate (mg/L)	17.97 ± 11.4	16.16 ± 10.57

Data are presented as mean ± standard deviation or median (interquartile range)

Abbreviation: ABI-Ankle-brachial index, ADPKD-autosomal dominant polycystic kidney disease; BMI-body mass index; BUN- blood urea nitrogen; CAVI-cardio-ankle vascular index; CKD-chronic kidney disease; eGFR-estimated glomerular filtration rate; FGF23-fibroblast growth factor 23; HDL-high density lipoprotein; hs-CRP-high sensitivity C reactive protein; iPTH-intact parathyroid hormone; LDL-low density lipoprotein; LVEF-left ventricular ejection fraction; LVH-left ventricular hypertrophy; LVMI-left ventricular mass index

Primary outcome

Changes in serum p-cresyl sulfate concentration

Serum p-cresyl sulfate levels at 12 and 24 weeks were 6.84 ± 5.4 and 7.77 ± 6.38 mg/L in sevelamer group and were 10.22 ± 7.78 and 13.24 ± 6.92 mg/L in calcium carbonate group (Figure 9).

The reductions of serum p-cresyl sulfate were compared between the sevelamer and calcium carbonate groups at 24-week follow-up (-4.67 ± 2.87 mg/L in sevelamer group and 3.64 ± 2.51 mg/L in calcium carbonate group), there was a significant reduction in the sevelamer group (p=0.04) (Figure 10).

In addition, serum p-cresyl sulfate levels were significantly decreased from baseline in the sevelamer group (p=0.01) but were unaltered in the calcium carbonate group (p=0.08) (Figure 10).

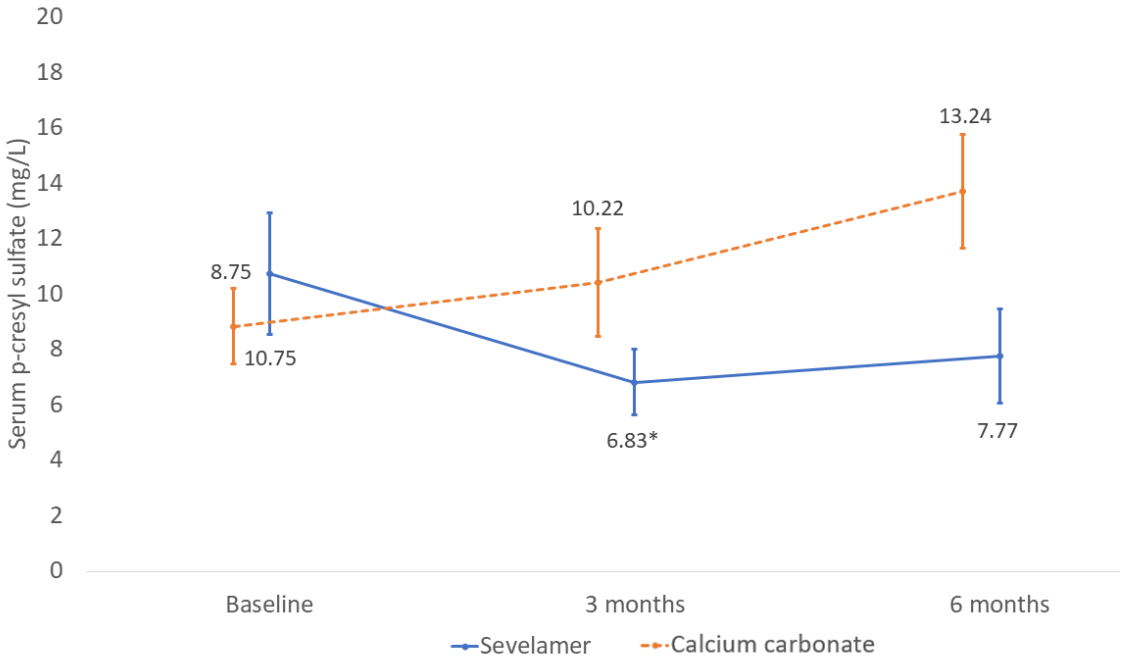

Figure 9 Serum p-cresyl sulfate levels in the sevelamer and calcium carbonate group during the 24-week follow-up period.

Data are expressed as mean and standard error, obtained using a linear mixed model.

(* significant difference within a group)

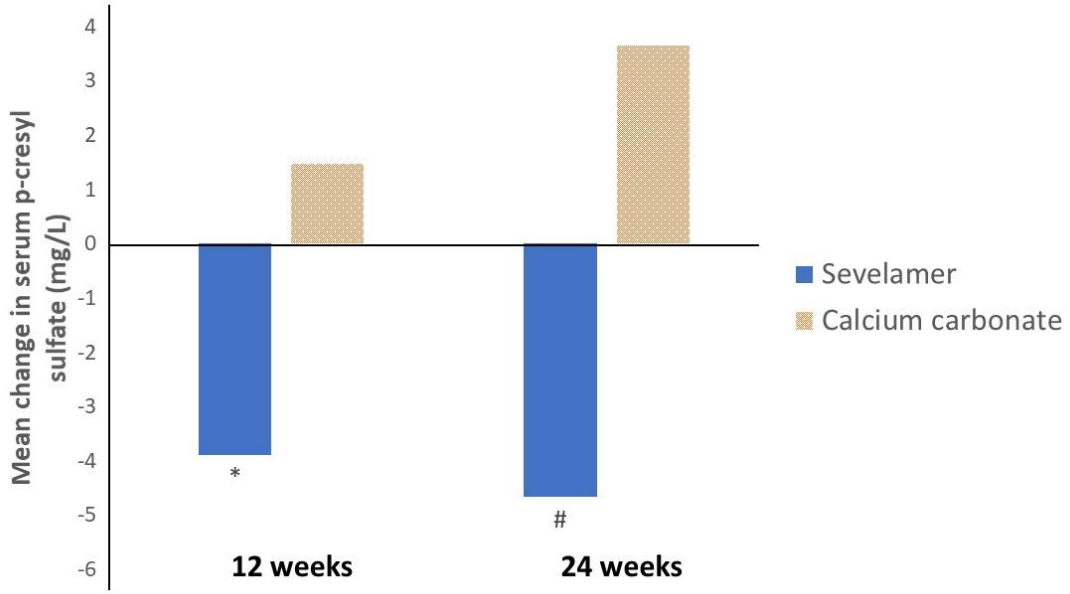

Figure 10 Mean change serum p-cresyl sulfate levels in the sevelamer and calcium carbonate groups during the 24-week follow-up period.

(* significant difference within a group; # significant difference between group)

Secondary outcomes

Change in serum indoxyl sulfate concentration

Serum indoxyl sulfate levels at baseline, 12 and 24 weeks were 17.97 ± 11.4, 17.13 ± 19.48, and 21.84 ± 22.1 mg/L in sevelamer group and were 16.16 ± 10.57, 16.85 ± 9.97, and 19.82 ± 14.41 mg/L in calcium carbonate group (Figure 11).

The changes during follow-up of serum indoxyl sulfate levels between sevelamer and calcium groups were not statistically different (p=0.36). There were no significant differences in serum indoxyl sulfate levels after 12 and 24 weeks, both in sevelamer (p=0.745 and p=0.398, respectively) and calcium carbonate groups (p=0.802 and p=0.49, respectively). (Figure 12).

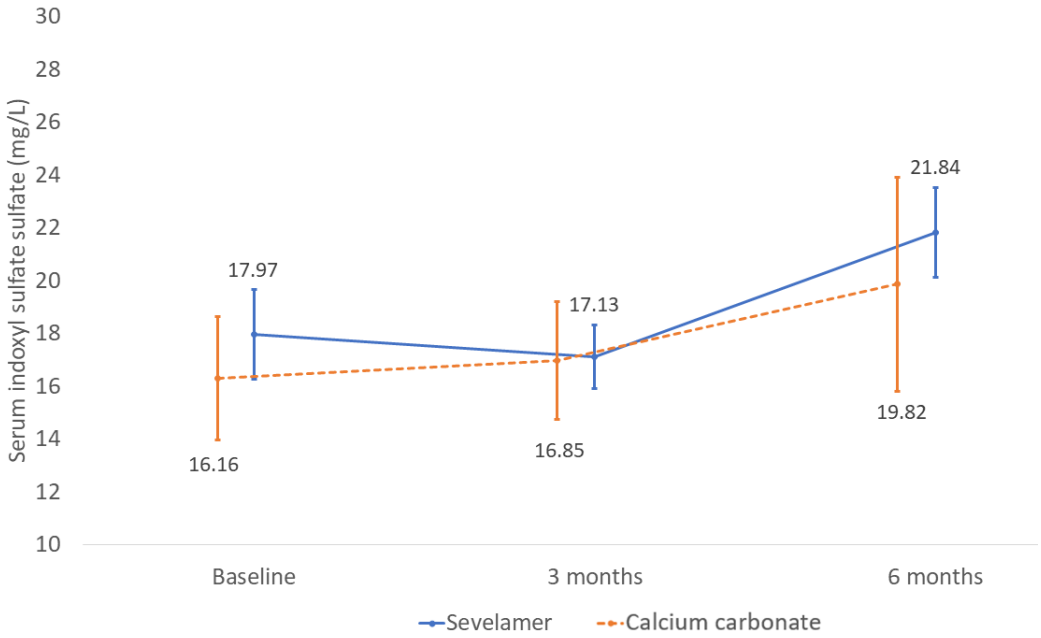

Figure 11 Serum indoxyl sulfate levels in the sevelamer and calcium carbonate groups during the 6-month follow-up period.

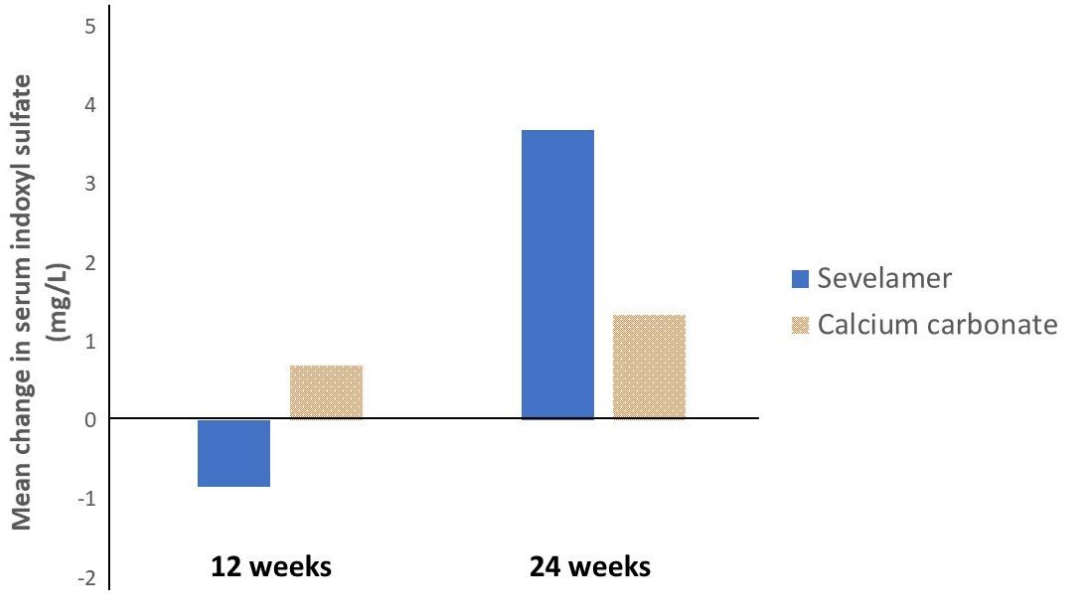

Figure 12 Mean change serum indoxyl sulfate levels in the sevelamer and calcium carbonate groups during the 24-week follow-up period.

Change in phosphate, calcium, PTH, and FGF 23

There were no significant differences in serum calcium, phosphate, and PTH levels during the study period between sevelamer and calcium carbonate treatment (Table 7). Interestingly, sevelamer group had a significant change of FGF23 levels from baseline when compared with calcium carbonate group at 24 weeks (p=0.01).

Using the Wilcoxon signed-rank test, there was no significant change of FGF23 levels from baseline and 24-week follow-up in sevelamer group. The values of median (IQR) were 47.19 (91.08) and 57.20 (122.27) pg/mL, respectively (p=0.58). However, FGF23 levels were significantly increased from baseline to 24-week follow-up in calcium carbonate group. The median (IQR) levels were 61.50 (83.73) and 106.07 (208.40) pg/mL, respectively, p=0.04) (Table 7).

Effects on renal function

There was no significant difference in the change of renal function between patients treated with sevelamer and calcium carbonate (mean difference between group -0.02; 95% CI -5.17 to 5.13 mL/min/1.73m2; p=0.99) (Figure 13).

During 24-week-follow-up, patients in both groups had significant reductions of renal function (p=0.04 in sevelamer group and p=0.001 in calcium carbonate group). In terms of dialysis initiation, three patients in the sevelamer group and four patients in the calcium carbonate group were initiated dialysis during the study. The dialysis initiation rate was estimated by the Kaplan-Meier method. The overall dialysis initiation at 24 weeks was 35%. There was no significant difference in cumulative incidence of dialysis initiation between sevelamer and calcium carbonate groups (hazard ratio 0.64 (95% CI 0.14 to 2.87; p=0.56) (Figure 14).

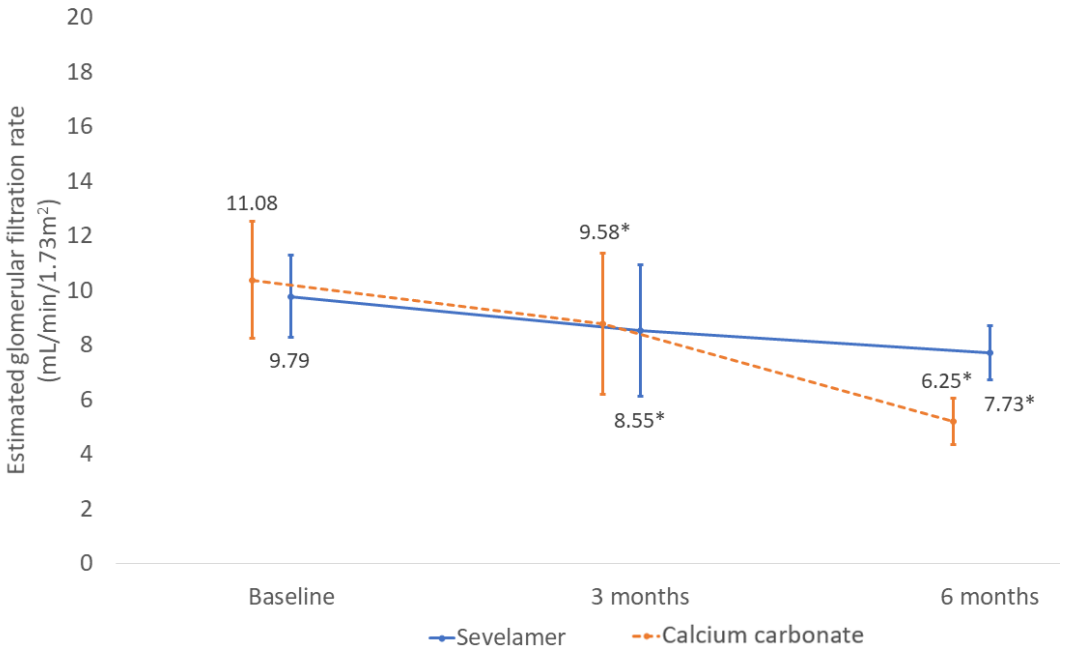

Figure 13 Mean change estimated glomerular filtration rates in the sevelamer and calcium carbonate groups during the 24-week follow-up period

(* significant difference within a group)

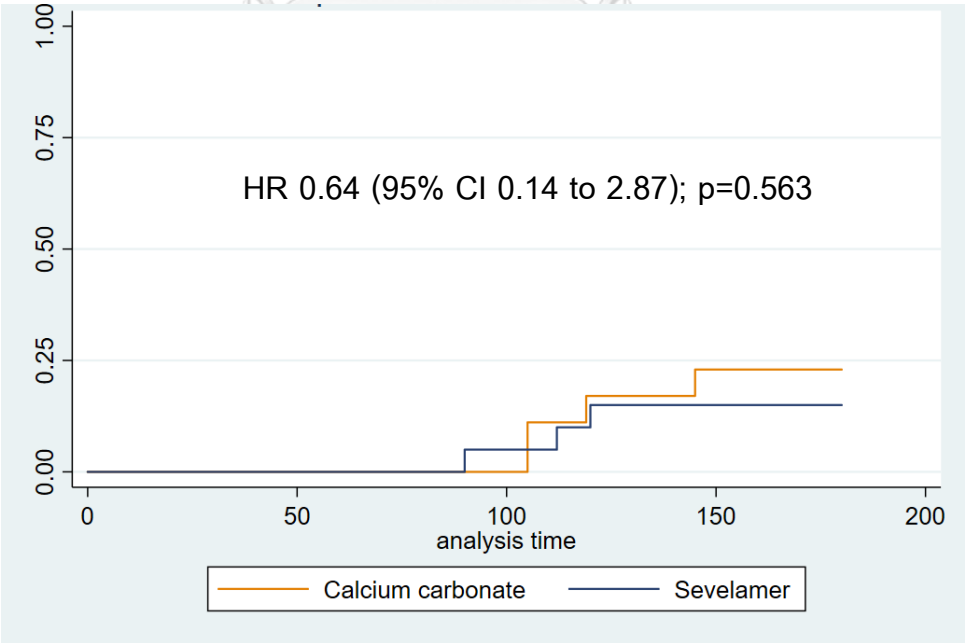

Figure 14 Cumulative incidence of dialysis initiation in patients treated with sevelamer and calcium carbonate

Effects on cholesterol, and hs-CRP levels

Treatment with sevelamer was associated with a significant reduction of LDL-cholesterol levels at 12 and 24 weeks compared with baseline (mean difference -41.67 mg/L; 95% CI -56.5 to -26.56 mg/L; p<0.001 and -42.74 mg/L; 95% CI -65.98 to -19.25; p<0.001, respectively). The reduction effect was not significant between 12 and 24 weeks. There were no significant changes in serum LDL-cholesterol levels after receiving calcium carbonate at 12 and 24 weeks (Table 7).

Treatment with sevelamer did not alter hs-CRP levels. The median (IQR) of hs-CRP levels in sevelamer at baseline and 24 weeks were 0.81 (0.96) and 1.03 (5.95), respectively. There was no significant change in hs-CRP levels analyzed by the Wilcoxon signed-rank test (p=0.07). Compared with calcium carbonate, a significant change in hs-CRP levels between the two groups was not observed (p = 0.643).

Effect on vascular stiffness and peripheral arterial disease

There was no significant change in CAVI score between baseline and 24-week follow-up in sevelamer and calcium carbonate groups (mean difference -0.75; 95% CI -0.26 to 0.11; p=0.4 and -0.17; 95%CI 0.36 to 0.01; p=0.09). Also, a significant difference between the groups was not observed (p=0.42). Similarly, there were no significant differences in ABI changes between sevelamer and calcium carbonate treatment (mean difference 0.004; 95% CI -0.6 to 0.69; p=0.89) (Figure 15).

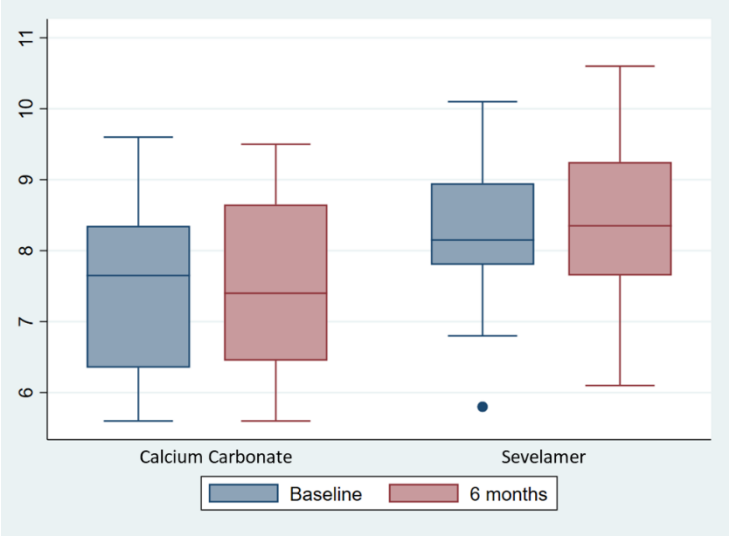

Figure 15 Cardio-ankle vascular index in patients treated with sevelamer and calcium carbonate at baseline and 24-week follow-up

Table 7 Laboratory parameters during the follow-up period in two groups of treatment

Parameters	Sevelamer			Calcium carbonate		
	Baseline	12 weeks	24 weeks	Baseline	12 weeks	24 weeks
Protein bound uremic toxins						
Serum p-cresyl sulfate (mg/L)	10.75 ± 9.84	6.84 ± 5.4*	7.77 ± 6.38#	8.75 ± 5.36	10.22 ± 7.78	13.24 ± 6.92
Serum indoxyl sulfate (mg/L)	17.97 ± 11.4	17.13 ± 19.48	21.84 ± 22.1	16.16 ± 10.57	16.85 ± 9.97	19.82 ± 14.41
CKD-MBD parameters						
Calcium (mg/dL)	8.96 ± 0.8	8.89 ± 0.77	8.65 ± 1.04	8.88 ± 1.45	9 ± 0.82	8.85 ± 1.4
Phosphate (mg/dL)	5.50 ± 0.78	4.85 ± 0.99	5.4 ± 1.64	5.39 ± 0.44	5.14 ± 0.98	6.05 ± 2.41
iPTH (pg/mL)	336.5 ± 184.05	319.85 ± 199.78	357.3 ± 252.86	303.78 ± 225.71	317.72 ± 233.41	339.33 ± 249.88
FGF23 (pg/mL)	47.19 (91.08)	53.18 (230.28)	57.20 (122.27)#	61.50 (83.73)	180.63 (212.11)*	106.07 (208.4)*

Nutrition parameters						
Albumin (g/dL)	3.94 ± 0.44	4.68 ± 3.63	3.85 ± 0.55	3.87 ± 0.35	3.98 ± 0.38	3.89 ± 0.42
LDL cholesterol (mg/dL)	112.89 ± 57.5	72.55 ± 32.56*	72.37 ± 47.65#	89 ± 31.81	83.44 ± 18.38	77.91 ± 25.92
HDL cholesterol (mg/dL)	40.97 ± 14.5	42.58 ± 16.54	45.21 ± 16.76	42.68 ± 13.56	44.67 ± 13.45	41.1 ± 13.43
Dietary protein intake (g/kg/day)	0.72 ± 0.24	0.68±0.12	0.71 ±0.11	0.70 ± 0.19	0.72 ±0.24	0.68±0.15
Renal function						
BUN (mg/dL)	69.1 ± 16.37	73 ± 22.44	75.9 ± 24.8	68.43 ± 19.5	82.5 ± 26.3	91.4 ± 23.6
Creatinine (mg/dL)	6.51 ± 3.07	6.95 ± 3.22	8.89 ± 6.16	6.03 ± 2.61	7.89 ± 4.13	10.52 ± 6.6
eGFR (mL/min/1.73m^2)	9.79 ± 6.72	8.55 ± 5.0*	7.73 ± 3.89	11.08 ± 8.86	9.58 ± 10.29*	6.25 ± 3.07*
Anemia and inflammatory markers						
Hemoglobin (g/dL)	9.76 ± 1.07	9.55 ± 1.23	9.28 ± 0.83	9.44 ± 1.14	9.34 ± 1.30	8.84 ± 1.8
Hs-CRP (mg/L)	0.81 (0.96)	0.98 (2.37)	1.03 (5.95)	0.8 (2.75)	0.96 (1.89)	2.23 (3.55)
Vascular stiffness parameters						
ABI	1.1 ± 0.10	N/A	1.1 ± 0.1	1.09 ± 0.94	N/A	1.1 ± 0.08
CAVI	8.36 ± 1.12	N/A	8.25 ± 1.22	7.47 ± 1.28	N/A	7.54 ± 1.3

Data are presented as mean±sd, median(IQR)

Abbreviation: ABI- ankle-brachial index; BUN- blood urea nitrogen; CAVI-cardio-ankle vascular index; eGFR-estimated glomerular filtration rate; FGF23-fibroblast growth factor 23; HDL-high density lipoprotein; hs-CRP-high sensitivity C reactive protein; iPTH-intact parathyroid hormone; LDL-low density lipoprotein

* p< 0.05 within a group; # p< 0.05 between group

Correlations between protein-bound uremic toxins and clinical and biochemical parameters

Inverse correlation of baseline p-cresyl sulfate and indoxyl sulfate levels with baseline renal function were significantly observed with baseline renal function (r = -0.33; p=0.049 and r = -0.74; p = 0.001) (Figure 16, 17). There was no significant association between baseline serum p-cresyl sulfate and indoxyl sulfate levels and eGFR changes during the study.

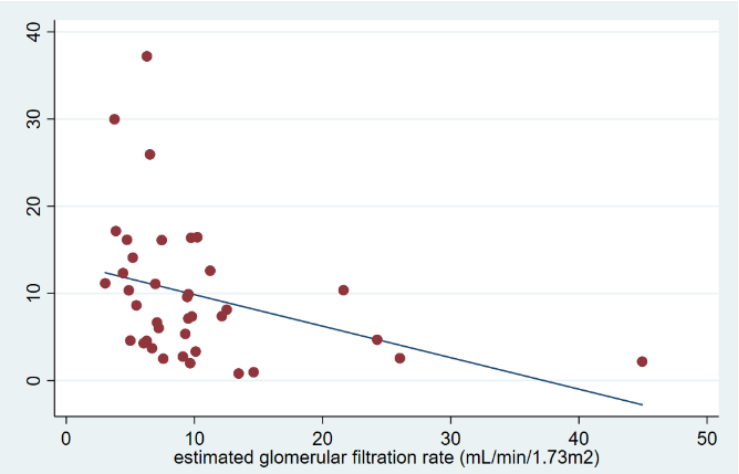

Figure 16 Correlation between baseline renal function and serum p-cresyl sulfate

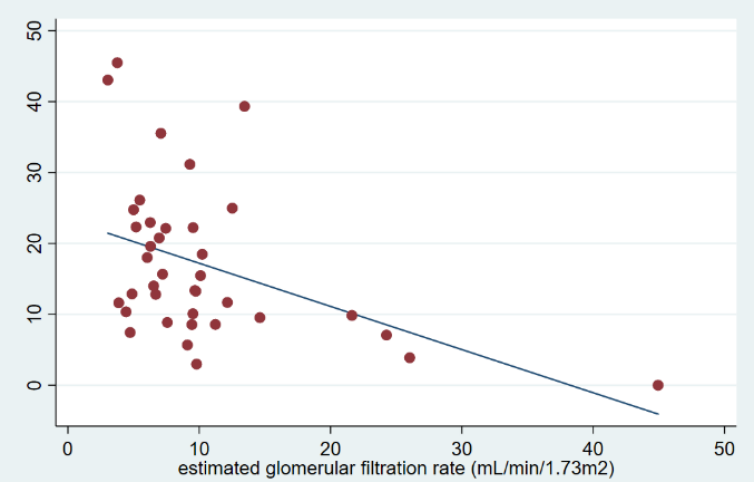

Figure 17 Correlation between baseline renal function and serum indoxyl sulfate

Table 8 shows the correlations between p-cresyl sulfate, indoxyl sulfate, and independent variables. Serum p-cresyl sulfate was significantly associated with history of cardiovascular disease (r = 9.26; p = 0.007), creatinine (r = 1.08; p = 0.017), phosphate (r = 4.30; p = 0.036), calcium (r = -4.73; p = 0.002) and indoxyl sulfate levels (r = 0.25; p = 0.031). Serum indoxyl sulfate was positively correlated with cardiovascular disease (r = 10.74; p = 0.025), creatinine (r = 2.91; p < 0.001), and phosphate levels (r = 6.46; p = 0.02) and was negatively correlated with calcium levels (r = -4.94; p = 0.022).

Table 8 Correlations between serum p-cresyl sulfate and indoxyl sulfate levels and baseline clinical and biochemical characteristics

	P-cresyl sulfate		Indoxyl sulfate	
Variables	r	p-value	r	p-value
Age	0.08	0.376	-0.07	0.535
Cardiovascular disease	9.26	0.007	10.74	0.025
Creatinine	1.08	0.017	2.91	<0.001
eGFR	-0.33	0.049	-0.77	<0.001
Phosphate	4.30	0.036	6.46	0.02
Calcium	-4.73	0.002	-4.94	0.022
PTH	0.01	0.126	0.02	0.053
Indoxyl sulfate	0.25	0.031	0.48	0.031
FGF-23	0.00007	0.918	-0.0003	0.742
Hemoglobin	-1.09	0.363	-2.29	0.159
Albumin	-0.66	0.844	-0.37	0.936
LVEF	-0.12	0.342	-0.06	0.726
LVH	-0.84	0.837	1.37	0.813
CAVI	1.06	0.398	1.88	0.241
ABI	4.74	0.755	25.27	0.188

Abbreviation: ABI- ankle-brachial index; CAVI-cardio-ankle vascular index; eGFR-estimated glomerular filtration rate; FGF23-fibroblast growth factor 23; PTH-parathyroid hormone

Follow-up data

All patients had good adherence to dietary advice. The mean DPI were ranged from 0.68 to 0.72 g/kg/day during the study period. More than 90 percent of patients had excellent adherence medication according to pill count.

Seven patients (17.5%), three of whom were initially assigned to the sevelamer group and the remaining 4 patients were in the calcium carbonate group, indicated renal replacement therapy during the study. All patients started dialysis after a 12-week follow-up visit with certain indications (five patients developed poor appetite and nausea, and two patients had clinical volume overload). There was no emergency dialysis initiation. No patients had a cardiovascular event or died during the follow-up period.

Adverse Events

One modest gastrointestinal side effect was reported in a patient receiving sevelamer. None of the patients had hypophosphatemia or hypercalcemia in both groups.

CHAPTER V
DISCUSSION

In this study, we explored the effects of sevelamer, an anion exchange resin which is a widely used non-calcium-based phosphate binder, on the p-cresyl sulfate and several uremic toxins reducing ability. The study was performed in pre-dialysis CKD patients with hyperphosphatemia and compared with calcium carbonate, another phosphate binding agent. Randomization was satisfactory in that baseline characteristics between sevelamer and calcium carbonate groups were comparable. During the 24-week follow-up period, the compliance of the study protocol was excellent, with more than 95 percent of patients receiving intervention according to the protocol.

This RCT is the first study to demonstrate the lowering effects of sevelamer on serum p-cresyl sulfate level compared with calcium carbonate therapy. The mean difference of serum p-cresyl sulfate between the two groups was -5.61±2.73 mg/L; p=0.04. Besides, sevelamer could effectively reduce LDL-cholesterol and FGF23 levels compared with calcium carbonate. However, there were no significant differences in serum indoxyl sulfate and hs-CRP levels after treatment.

The human intestine is known as the habitat of more than 100 trillion micro-organisms which provide several metabolic products and allocate the human immune system. There are both qualitative and quantitative alterations in the composition of gut microbiota in CKD patients due to decreased consumption of dietary fibers, multiple drug uses, metabolic acidosis, intestinal wall edema, and accumulation of uremic toxins[71]. The higher number of pathogenic microbes and increased intestinal permeability in CKD patients contribute to the elevation of gut-derived uremic toxins such as p-cresyl sulfate and indoxyl sulfate[72]. Therefore, the rise of serum p-cresyl sulfate level in CKD patients results from decreased renal excretion and increased production due to the change in intestinal microbiome, which promotes the production of these compounds. A previous *in vitro* study showed that sevelamer could directly sequester p-cresol, a precursor of p-cresyl sulfate. However, the lowering effect was not observed in the CKD mouse model.

Only a few clinical studies have evaluated the impact of sevelamer on uremic toxins. A small cohort study revealed a significant reduction of serum p-cresyl sulfate in hemodialysis patients[63]. Previous RCTs that investigated the effect of sevelamer reported conflicting results (Table 9). Riccio et al. showed that 1,600 mg of sevelamer carbonate effectively reduced serum p-cresyl sulfate in pre-dialysis CKD patients compared with placebo after 12 weeks of treatment[64]. In comparison, Bennis et al. reported an insignificant association between a 12- week of treatment with 4,800 mg of sevelamer carbonate and serum p-cresyl sulfate and indoxyl sulfate changes in CKD stage 3b and 4 compared with placebo[65]. The different results might be explained by the disparities in populations, baseline renal function and serum p-cresyl sulfate level, and follow-up time (Table 9)

Our study, which was the first to compared sevelamer with calcium-based phosphate binder, was performed in very advanced pre-dialysis CKD patients. Ninety percent of our patients were CKD stage 5 and the mean eGFR was 10.4±7.73 mL/min/1.73m^2 which was obviously lower than previous studies (mean eGFR was 38.7 and 27 mL/min/1.73m^2). The different baseline renal function resulted from the inclusion criteria as hyperphosphatemia in our study. Despite the declined renal function, patients with early-stage CKD could control the serum phosphate level within the normal range by increasing phosphate renal excretion. Pre-dialysis CKD patients usually develop hyperphosphatemia when they are late stage 4 or stage 5 CKD[73]. As our patients were advanced CKD, the baseline serum p-cresyl sulfate was higher than the previous study[64]. Moreover, in this study, patients received the intervention and were followed up for 24 weeks which were longer than earlier reports. According to our results, the reduction of serum p-cresyl sulfate in the sevelamer group was initially observed at 12 weeks; however, the significant difference between the two groups was revealed at 24 weeks. More impaired renal function with a longer follow-up period might explain the positive effects of sevelamer observed in our study.

We also explored the lowering effects of sevelamer on other uremic toxins and substances, including indoxyl sulfate, FGF23, and hs-CRP. We found no significant

change of serum indoxyl after receiving sevelamer or calcium carbonate. The result was supported by several previous studies. In an early *in vitro* study, Bennis et al. revealed that sevelamer did not have the ability to chelate indole, the precursor of indoxyl sulfate, regardless of the pH value[65]. A cross-over interventional study by Brandenburg et al. investigated the effect of sevelamer on serum indoxyl sulfate level in 41 hemodialysis patients. After 8 weeks of sevelamer hydrochloride and calcium acetate, there was no significant change in serum indoxyl sulfate concentration[74]. Very recently, a multicenter, double-blind, placebo-controlled, randomized clinical trial reported insignificant indoxyl sulfate reduction after sevelamer treatment in 78 pre-dialysis CKD patients[65].

FGF23 was another uremic toxin that could be effectively reduced by sevelamer in this study. The primary function of FGF23 in CKD patients is to enhance renal phosphate excretion. FGF23 level continuously rises during the progression of CKD in order to maintain a normal phosphate level. Several studies illustrated correlations between high FGF23 levels and numerous deleterious effects, including left ventricular hypertrophy, vascular calcification, and mortality[50, 75]. As phosphate is an important stimulating factor of FGF23 production, phosphate binders are expected to be an efficacious lowering modality of FGF23. However, previous data showed that not all phosphate binders could reduce FGF23 levels. A recent systematic review and meta-analysis supported the positive effect of sevelamer on FGF23 in our study. Takkavatakarn et al. reported a significant decrease of FGF23 in CKD patients receiving sevelamer either compared with calcium carbonate or placebo. In contrast, there was no significant reduction of FGF23 level in patients treated by lanthanum, another non-calcium-based phosphate binder when compared with placebo[55]. These findings demonstrate that the effect of sevelamer on FGF23 reduction could not be explained by the lowering phosphate ability of phosphate binders but might result from the pleiotropic effects of sevelamer. Several studies have indicated a positive correlation between inflammatory markers such as TNF-α and FGF23 levels[76, 77]. Additionally, inflammation in CKD rats reduces the expression of klotho introducing a mechanism for the development of renal resistance to FGF23[78]. Golmohamadi et al. reported that CKD rats treated with sevelamer had an elevation in

serum levels of klotho that could obviate renal resistance to FGF23 and reduce FGF23 levels[79].

Previous data showed the potency of sevelamer in diminishing endotoxin, a glycolipid component of the gram-negative cell wall which is a potent stimulus for proinflammatory cytokine production[80]. In advanced CKD, bacterial translocation from the gastrointestinal tract is a significant source of endotoxin[81]. According to the negative charge property, sevelamer could effectively sequester endotoxin in both *in vitro* and *in vivo* studies[82]. A previous observational study showed that sevelamer could lessen endotoxin and consequently decrease proinflammatory cytokines and C-reactive protein in hemodialysis patients[83]. However, the reduction of hs-CRP was not observed in our study. A possible explanation for the discrepancy among the studies might be the difference in population and baseline hs-CRP levels of the patients. Indeed, systemic inflammation increases as the renal function progressively declines, especially in dialysis patients. The pathophysiology involved in intensifying chronic inflammation has been described as multifactorial factors, including exposure to catheter and dialysis membrane, alteration of gut microbiota, intravenous iron supplement, and retention of several uremic toxins[84]. Previous studies that observed the reduction of hs-CRP after sevelamer treatment were performed only in hemodialysis patients. In contrast, our study and recent RCTs that explored this outcome in pre-dialysis CKD patients did not demonstrate the significant difference between sevelamer and control groups[64]. However, it should be counted that our sample size may be too small to detect the difference in secondary outcomes.

P-cresyl sulfate is known as a vascular toxin since it induces inflammation and oxidative stress via leukocyte activation, causing vascular endothelial injury and reduction of nitric oxide production[19, 20, 85]. A previous systematic review of 27 studies both *in vitro* and *in vivo* reported the positive correlations between serum p-cresyl sulfate level and vascular dysfunction together with aortic calcification[21]. The p-cresyl sulfate level was also significantly associated with cardiovascular events and all-cause mortality in CKD patients[4]. The reduction of serum p-cresyl sulfate is expected to be a promising strategy

to improve cardiovascular outcomes which are responsible for the major cause of death in CKD patients. The clinical trial focused on long-term clinical outcomes was lacking. This study measured the vascular stiffness by cardio-ankle vascular index (CAVI) at baseline and end-of-the study; however, a significant change of patients' vascular stiffness was not observed. We also evaluated the renal outcomes, including renal progression and incidence of dialysis initiation. There were no significant differences in renal outcomes between sevelamer and calcium carbonate groups. Since ninety percent of participants in this study were stage 5 CKD with the mean eGFR about 10 mL/min/1.73m^2, it might be too late to manipulate renal progression. Long term follow-up study in earlier stage CKD is still warranted.

This is the first RCT focusing on sevelamer's effect on serum p-cresyl sulfate reduction in very advanced stage pre-dialysis CKD patients with hyperphosphatemia who indicated phosphate binders according to current guidelines. We provide novel advantages of sevelamer over calcium-based phosphate binders. Participants had good compliance with dietary counseling and well-controlled protein and phosphate intake through the study period which are important factors influencing gut-derived uremic toxins production. In addition, intervention adherence measured by pill counts was excellent. There are some limitations in this study. First, the number of participants is relatively small. Although we performed appropriate statistical calculations and the primary outcome could achieve statistical significance, the power for analysis of secondary outcomes was limited. The potency of sevelamer on lowering the other substance such as indoxyl sulfate is needed in further study. Second, our study did not represent a long follow-up period, as such we might miss detecting the effect of sevelamer on clinical outcomes, including vascular stiffness and cardiovascular events.

Table 9 Comparison between previous randomized controlled trials and our study

	Riccio et al. 2018[64]	Bennis et al. 2019[65]	The present study 2021

Country	Italy	France	Thailand
Study design	Randomized controlled trial	Secondary analysis of randomized controlled trial	Randomized controlled trial
Number of patients	60	78	40
Inclusion criteria	Pre-dialysis CKD stage 3-5	Pre-dialysis CKD stage 3b-4 (Patients included in FGF23 Reduction Efficacy of a New Phosphate Binder in Chronic Kidney Disease RCTs; FRENCH study 2017[86])	Pre-dialysis CKD patients with hyperphosphatemia (> 5 mg/dL)
CKD staging	CKD stage 3 – 60% CKD stage 4 – 35% CKD stage 5 – 5%	N/A	CKD stage 4 - 10 % CKD stage 5 – 90%
Baseline renal function; eGFR (mL/min/1.73m^2)	38.7 ± 14.6	27.0 ± 9.1	10.4±7.73
Baseline serum phosphate (mg/dL)	4.35 ± 0.6	3.84 ± 0.05	5.32 ± 0.87
Baseline p-cresyl sulfate (mg/L)	7.3 ± 4.0	10.65 (6.05; 17.69)	9.8 ± 7.9
Intervention	Sevelamer 1600 mg per day	Sevelamer 4,800 mg per day	Sevelamer 2,400 mg per day
Comparator	Placebo	Placebo	Calcium carbonate
Follow-up time	12 weeks	12 weeks	24 weeks
Primary outcome	Treatment with sevelamer resulted significantly lower serum p-cresyl sulfate level compared to	No statistically significant differences between the sevelamer and placebo group in the	Treatment with sevelamer resulted significantly lower serum p-cresyl sulfate level compared to

	placebo (-3.89 mg/L; p < 0.001)	changes in serum p-cresyl sulfate	placebo (-5.61±2.73 mg/L; p=0.04)
Secondary outcomes	Significant reduction of LDL-cholesterol, hs-CRP, and phosphate in sevelamer group	- Significant reduction of LDL-cholesterol in sevelamer group - No statistically significant differences between sevelamer and placebo group in the changes in serum indoxyl sulfate, FGF23, and phosphate	- Significant reduction of LDL-cholesterol and FGF 23 levels in sevelamer group - No statistically significant differences between sevelamer and calcium carbonate group in the changes in serum indoxyl sulfate and phosphate

Abbreviation: CKD-chronic kidney disease; FGF23-fibroblast growth factor 23; hs-CRP-high-sensitivity C-reactive protein; LDL-low-density lipoprotein

Conclusions

In conclusion, sevelamer could effectively reduce serum p-cresyl sulfate and FGF23 levels and attenuate lipid profiles in pre-dialysis CKD patients with hyperphosphatemia. The differences in serum indoxyl sulfate level, renal progression, and dialysis initiation were not observed between sevelamer and calcium carbonate treatment. Our data suggest the additional benefits of sevelamer over calcium-based phosphate binder in cardiovascular protection by reducing cardiovascular toxic substances in CKD patients.

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