Effect of Sevelamer on Serum Levels of Klotho and Soluble Tumor Necrosis Factor-like Weak Inducer of Apoptosis in Rats With Adenine-induced Chronic Kidney Disease

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Introduction. Nontraditional risk factors for cardiovascular disease (CVD), including mineral disorder, high fibroblast growth factor 23 (FGF23), low klotho, and low soluble TWEAK could predict the incipient risk of CVD in chronic kidney disease (CKD). The present study evaluates the effect of sevelamer on soluble tumor necrosis factor-like weak inducer of apoptosis (TWEAK), and klotho levels in adenine-induced CKD rats.

Methods and Materials. Normal control rats without sevelamer were compared with 3 groups of adenine-induced CKD rats, including CKD rats without sevelamer, CKD rats treated with 3% sevelamer, and rats receiving adenine and 3% sevelamer concurrently. After 4 weeks of sevelamer treatment, serum levels of klotho and soluble TWEAK were measured, along with biochemical parameters related to kidney function.

Results. Sevelamer significantly reduced serum levels of phosphate and increased serum levels of klotho and soluble TWEAK. Decreased levels of phosphate were negatively correlated with elevated levels of klotho and soluble TWEAK (r = -0.70, *P* = .003; r = -0.58, *P* = .02; respectively) in serum.

Conclusions. Sevelamer successfully reduced serum levels of phosphate, and meanwhile, it led to an elevation in serum levels of klotho and soluble TWEAK in rat models of CKD.

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INTRODUCTION

Chronic kidney disease (CKD), a common problem in the world, is an independent risk factor for cardiovascular disease (CVD) events.[1,2] Traditional CVD risk factors do not fully predict the risk of future cardiovascular events in CKD patients.[3] Nontraditional risk factors like abnormal mineral metabolism, vitamin D deficiency, and hyperparathyroidism, grouped together as CKD-related mineral and bone disorders may better clarify the risk of incipient CVD in CKD patients.[4] Pathogenesis of CKD-related mineral and bone disorders has been attributed to the variations in calcium and phosphate metabolism.[4,5] Studies have shown that various CKD-related complications such as vascular calcifications and mortality rates are accompanied with high serum phosphate levels.[6]

It has been demonstrated that increased levels of fibroblast growth factor 23 (FGF23), as a phosphaturic hormone, directly acts on the kidney in response to phosphate overload in healthy individuals and in patients with CKD.[4] Klotho is a cell membrane coreceptor and an anti-aging hormone mainly synthesized in the kidneys,

and the action of FGF23 is mediated by binding to α-Klotho, an FGF cell-surface receptor.[7] It is believed that the increase in serum FGF23 levels is probably due to a reduced klotho expression in the kidneys, which enhances the resistance to FGF23.[8,9] One key action of FGF23 and Klotho is to protect from phosphate overloads; FGF23 and Klotho decrease tubular phosphate reabsorption, causing phosphaturia and declines in intestinal phosphate absorption.[10]

Tumor necrosis factor-like weak inducer of apoptosis (TWEAK) is a cytokine of the tumor necrosis factor (TNF) superfamily, and circulates in plasma as a soluble form. Soluble TWEAK mediates multiple biologic effects including cellular growth, proliferation and migration, osteoclastogenesis, angiogenesis, and apoptosis upon binding to its receptor, Fn14.[11] Although basal Fn14 expression is normally low, it is upregulated during kidney injury.[12] The decreased soluble TWEAK levels could be a consequence of upregulated Fn14 expression in injured vessels.[13] Serum soluble TWEAK concentration decreases progressively with increasing CKD stage.[14,15]

In a study conducted by Mendoza and coworkers, a positive correlation between serum FGF23 and inflammatory markers interleukin-6 (IL-6), C-reactive protein (CRP), TNF-α, and fibrinogen in CKD patients was noted, which underlines the relationship between systemic inflammation and FGF23 regulation.[16] Kidney inflammation as an early feature of CKD may be induced by albuminuria, and this inflammation is an important factor in downregulating klotho expression in renal proximal tubules.[10,17,18] Klotho, as a key regulator of phosphate balance, has anti-inflammatory and antioxidant properties and the role of phosphate has been shown in ageing.[10] However, the potential relationship between inflammation and phosphate requires further investigations.

From this perspective, CKD can be considered as a state of hyperphosphatemia, low soluble TWEAK, and low Klotho. Klotho plays a central role in the pathogenesis of CVD and could be considered a potential therapeutic target for improving survival rates in patients with CKD.

Several classes of phosphate binders such as sevelamer hydrochloride are able to decline serum FGF23 levels.[19,20] In Lin and colleagues' study, the increase in serum Klotho was accompanied by a reduction in FGF23 in chronic hemodialysis patients.[21] Sevelamer treatment in CKD and dialysis patients has led to improvement in inflammatory parameters, ie, increase in serum levels of albumin, and decrease in CRP, IL-10, and TNF-α levels.[22-25] We considered recent research that suggested phosphate, soluble TWEAK, and Klotho field could be a therapeutic target in CKD and hypothesized that sevelamer hydrochloride, as a phosphate binder, led to improve this route. In this study, we used a rat model of adenine-induced kidney failure,[26] in order to examine the effect of sevelamer hydrochloride on serum levels of klotho and soluble TWEAK in rats with CKD.

MATERIALS AND METHODS

Animals

A total of 35 male Wistar rats with the mean weight of 245 ± 28 g were used in the study. Ethics approval of the study protocol was obtained from the Ethics Board of Tabriz University of Medical Sciences, Experimental Animals Laboratory (IR.TBZMED.REC.1395.1084). Animal's rights were adhered to throughout the study according to the statement issued by the board.

Study Design

After an acclimatization period of 1 week, the animals were divided into 4 groups (Table 1). The first group (n = 8) continued to receive the standard pellet (normal diet) without any intervention. In group 2 and 3, the diet received by the rats was compounded with 0.75% adenine (Sigma, St Louis, Missouri, USA) for 4 weeks. Kidney failure was induced in these rats by feeding 0.75% adenine-containing diet in 4 weeks.[26] Tail vein blood samples

Table 1. Experimental Protocol

Group	First 4 Weeks	Second 4 Weeks
Group 1: normal control	Normal diet	Normal diet
Group 2: kidney failure control	Adenine	Normal diet
Group 3: 3% sevelamer	Adenine	3% sevelamer
Group 4: adenine + 3% sevelamer	Adenine + 3% sevelamer	Normal diet

were collected to measure the serum levels of creatinine and blood urea nitrogen (BUN) in order to confirm CKD on the day 28. These adenine-induced CKD rats were divided into 2 groups (groups 2 and 3) by matching for body weight, serum phosphate, calcium, BUN, and creatinine levels. Group 2 (n = 10) was adenine control group receiving normal diet with no sevelamer. Group 3 (n = 8) was treated with 3% sevelamer hydrochloride mixed into normal diet for 4 weeks. The animals in group 4 (n = 9) received adenine and 3% sevelamer hydrochloride together in diet.

The rats were anesthetized by ketamine (100 mg/kg, intraperitoneal) to collect venous blood samples on the day 60 of the experiment. Sera were separated by centrifugation at 4000 g for 10 minutes and were stored at -80°C.

Determination of Serum Parameters

Serum levels of phosphate, BUN, creatinine, total protein, and albumin were determined using a clinical chemistry analyzer (Cobas Mira, Roche, Basel, Switzerland). Serum soluble TWEAK and klotho levels were measured using an enzyme-linked immune sorbent assay kit (BT, Bioassay Technology Laboratory).

Statistical Analysis

Data were analyzed using the SPSS software (Statistical Package for the Social Sciences, version 18.0, IBM Corp, New York, NY, USA)and were expressed as mean ± standard deviation. An unpaired *t* test was used to compare the adenine-control group with the normal-control group. The correlation between parameters was analyzed using the Pearson correlation test. Differences between groups were analyzed using the 1-way analysis of variance. *P* values less than .05 were considered significant.

RESULTS

As demonstrated in Table 2, no significant change in body weights was noted between adenine- and sevelamer-receiving groups and normal control groups. Serum levels of BUN, creatinine, phosphate were examined. All parameters were significantly increased in adenine-induced CKD group as compared to normal rats. Creatinine and BUN levels were still high despite the treatment with 3% sevelamer as compared to day 28 of the study, though a slight decrease in their levels were observable. A significant decrease in serum levels of phosphate were noted with 3% sevelamer (Table 3).[27] On the other hand, serum albumin levels that were decreased in CKD rats demonstrated a significant elevation in the group treated with 3% Sevelamer, as has been reported in our previous work (Table 3).

As shown in Table 4, the CKD rats had significantly lower levels of serum klotho and soluble TWEAK levels compared with those in the normal rats. Soluble TWEAK levels were significantly increased after treatment with 3% sevelamer. Such an elevation was also noted in serum levels of klotho.

Correlation analyses revealed that in the CKD and 3% sevelamer-treated CKD groups, the decrease in serum phosphate levels were negatively correlated with elevated serum klotho and soluble TWEAK levels (r = -0.70, *P* = .003; r = -0.58, *P* = .02; respectively; Table 5).

DISCUSSION

Current study demonstrates that phosphate reducing effect of sevelamer might be associated with the increased serum levels of soluble TWEAK, klotho, and albumin. In our study, serum levels of creatinine and BUN were decreased by sevelamer, but not to a statistically significant extent, similar to the results obtained by Nagano and colleagues.[28] Sevelamer decreased serum levels of phosphate in the current study as supported by multiple previous studies. As indicated by Covic and colleagues, sevelamer treatment successfully decreased

Table 2. Effects of Sevelamer on Body Weight

	Study Groups			
Body Weight, g	Normal Control	Kidney Failure Control	3% Sevelamer	Adenine + 3% Sevelamer
0 weeks	219.5 ± 56.1	231.2 ± 41.0	221.6 ± 11.0	227.6 ± 12.6
4 weeks	260.2 ± 24.4	178.7 ± 21.6*	175.7 ± 18.0*	185.6 ± 20.6†
8 weeks	291.8 ± 26.8	225.6 ± 30.0	233.0 ± 19.9	193.6 ± 18.6

*$P < .001$ compared with normal control group
†$P < .05$ compared with kidney failure control group

Table 3. Effects of Sevelamer on Plasma Parameters

Plasma Parameters	Study Groups			
	Normal Control	Kidney Failure Control	3% Sevelamer	Adenine + 3% Sevelamer
Creatinine, mg/dL				
4 weeks	0.41 ± 0.10	2.30 ± 0.96*	2.28 ± 0.78*	2.34 ± 0.49*
8 weeks	0.47 ± 0.06	1.08 ± 0.73†	0.79 ± 0.21	...
Urea nitrogen, mg/dL				
4 weeks	40.50 ± 3.92	219.90 ± 54.80*	207.00 ± 64.79*	209.20 ± 39.14*
8 weeks	38.00 ± 5.39	99.60 ± 46.63†	79.50 ± 18.82	...
Phosphorus, mg/dL				
4 weeks	4.87 ± 0.46	8.10 ± 2.53*	7.98 ± 1.70*	4.98 ± 1.31
8 weeks	5.31 ± 0.44	8.09 ± 1.70*	5.91 ± 1.48§	...
Albumin, g/dL				
4 weeks	3.94 ± 0.20	3.43 ± 0.22†	3.49 ± 0.48†	3.66 ± 0.24
8 weeks	3.99 ± 0.24	3.56 ± 0.20†	3.87 ± 0.22§	...
Total protein, g/dL				
4 weeks	7.56 ± 0.34	7.39 ± 0.88	7.09 ± 0.53	7.24 ± 0.48
8 weeks	7.40 ± 0.44	6.82 ± 0.81	7.29 ± 0.62	...

*P < .001 compared with normal control group
†P < .01 compared with control group
§P < .05 compared with kidney failure control group

Table 4. Effects of Sevelamer on Serum Levels of Klotho and Soluble Tumor Necrosis Factor-like Weak Inducer of Apoptosis (TWEAK)

	Study Groups			
Parameter	Normal Control	Kidney Failure Control	3% Sevelamer	Adenine + 3% Sevelamer
Klotho, ng/mL	2.29 ± 0.55	1.24 ± 0.33*	1.97 ± 0.42†	1.86 ± 0.50†
Soluble TWEAK, ng/L	277.02 ± 74.96	147.76 ± 42.17*	256.80 ± 86.80†	214.99 ± 78.89

*P < .01 compared with normal control group
†P < .05 compared with kidney failure control group

Table 5. Correlations Between Parameters in Kidney Failure and 3% Sevelamer-treated Kidney Failure Groups*

Parameter	Klotho	Soluble TWEAK	Albumin
Phosphate	r = -0.70, P = .003	r = -0.58, P = .02	r = -0.54, P = .02
Klotho	…	r = 0.62, P = .01	r = 0.59, P = .02
soluble TWEAK	…	…	…
Albumin	…	r = 0.64, P = .007	…

TWEAK, tumor necrosis factor-like weak inducer of apoptosis.

serum levels of FGF23 together with phosphate.[29] Contrarily, the findings of other studies showed that it is possible that once overt hyperphosphatemia evolves, FGF23 levels may not be reduced by phosphorus reduction alone in CKD patients. In Spatz and coworkers' research, the patients treated with sevelamer carbonate did not have a significant change in plasma FGF23 levels despite a significant reduction in phosphorus.[30,31] This fact could be justified by referring to the mechanism of action of FGF-23; it has been shown that FGF23 downregulates the 1-α-hydroxylase enzyme in the kidney, causing a decline in the levels of active form of vitamin D with resultant decrease in intestinal phosphate absorption. Fibroblast growth factor 23 exerts these actions by binding to the FGF receptor-klotho complex in the kidney, and thus regulates the phosphorus homeostasis.[32] It is worth to note that in our experiment, reduced levels of klotho was found in induced CKD group, and sevelamer was able to counteract this effect by preserving serum levels of klotho. This scenario underlines that sevelamer not only affects phosphate but also has an impact on the klotho, the coreceptor of FGF23.

We noted a significantly decreased serum albumin levels in CKD rats. Earlier studies indicate that low levels of albumin are associated with increased levels of inflammatory markers such as IL-6, CRP, and TNF-α in CKD.[33-35] Serum albumin levels were significantly increased by sevelamer

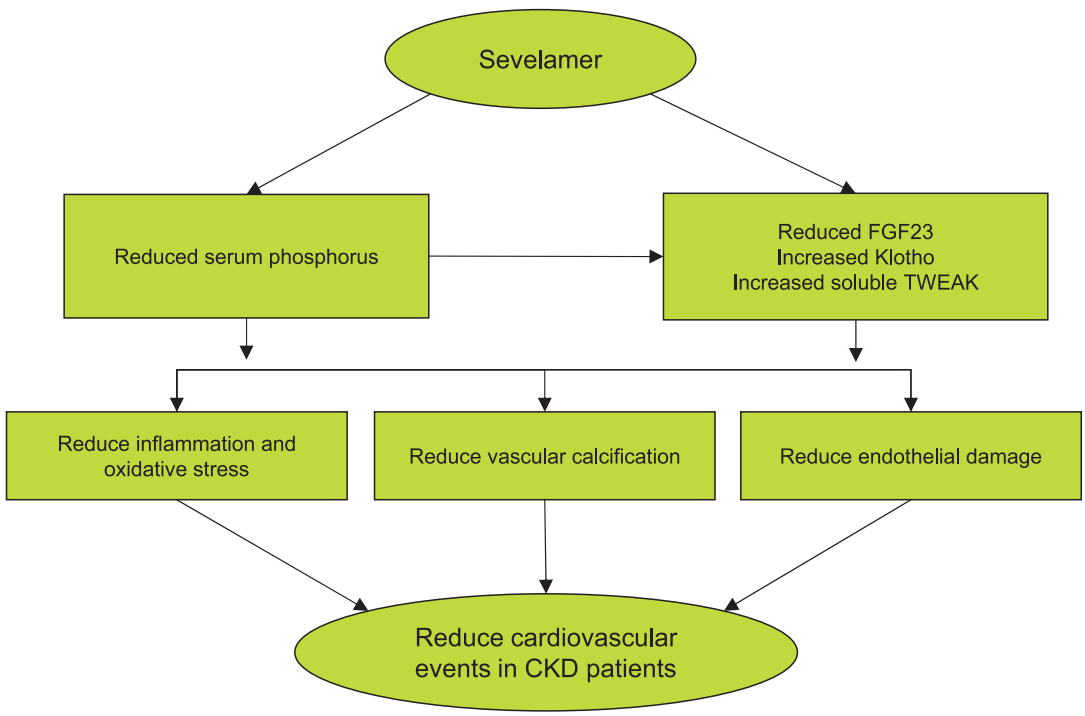
treatment in our study. In agreement with these results, Peres and colleagues showed that sevelamer significantly elevated albumin levels in serum, which was accompanied by a decline in the levels of TNF-α and CRP.[36]

Serum soluble TWEAK levels decreased in CKD rats as compared to normal ones in the present study. Similar results has been obtained by Fernández-Laso and colleagues, besides demonstrating that decreased circulating soluble TWEAK concentrations are independently associated with the development of coronary artery disease[37]; yet soluble TWEAK is a new nontraditional risk factor candidate of CVD.[38] The promising outcome of our study was to demonstrate that sevelamer treatment led to an elevation in serum soluble TWEAK levels.

There is one recent observation that TWEAK activates FGF23 receptors and thus these two proteins might have reciprocal effects on CVD. Soluble TWEAK activates Fn14 and declines the expression of klotho at both protein and mRNA levels. Furthermore, klotho expression was inversely correlated with Fn14 expression, bringing to mind that TWEAK, like TNF, may regulate klotho expression.

Conflicting results about sevelamer impact on inflammation has been published; while Hauser and colleagues suggests that sevelamer carbonate induces an anti-inflammatory effect, ie, reduces TNF-α levels,[39] and Kursat and coworkers reported that in CRF rats with kidney failure, sevelamer was able to reduce inflammatory markers,[40] no significant anti-inflammatory effects has been observed by Tzanno-Martins and colleagues, observing that no significant differences in blood cytokine levels including IL-1, IL-6, IL-10, and TNF-α develops. It should be noted, however, that trial duration of this study was relatively short.[41] Several studies have indicated a positive correlation between inflammatory markers such as TNF-α and circulating FGF23 in patients with CKD in which as FGF23 levels begin to elevate, the markers of inflammation also increase.[16,42]

Additionally, it has been shown that inflammation reduces the expression of klotho in the mouse kidney introducing a mechanism for the development of renal resistance to FGF23.[17,18] When referred to mechanistic studies,[8,9] it would be inferred that increased klotho could possibly obviate renal resistance to FGF23 and reduce its levels, so as evidenced in the present study there is a significant negative association between FGF23 and klotho.



Schema of the main effects sevelamer trend to reduce cardiovascular event in chronic kidney disease (CKD) patients. FGF23 indicates fibroblast growth factor 23 and TWEAK, tumor necrosis factor-like weak inducer of apoptosis.

Mechanistic understanding of the relationship between klotho and TWEAK is as follows: inflammatory cytokines such as TWEAK and TNF-α, downregulate klotho in renal tubular cells through nuclear factor-κβ pathway. Simultaneous increase in serum klotho and soluble TWEAK, perhaps reduce inflammation and oxidative stress and consequently alleviate endothelial injury. The schematic representation of this relationship is depicted in the Figure.

In summary, we demonstrated that phosphate lowering effect of sevelamer were associated with an increase in serum levels of klotho together with soluble TWEAK in adenine-induced CKD rats. As high levels of phosphate and low levels of klotho and soluble TWEAK are proposed as risk factors for CVD events in CKD patients, sevelamer with the observed ability to make the condition vice versa, could firmly be considered as a cardiovascular risk lowering agent in these group of patients. However, the experimental and preliminary nature of study necessitates findings to be confirmed in clinical trials with relatively large sample sizes. In addition, the exact contribution of each factor including klotho and soluble TWEAK to the development of CVD events should be clarified separately in such studies.

CONCLUSIONS

Sevelamer protected against deterioration of kidney function, reduced serum phosphate and elevated serum levels of klotho and soluble TWEAK in adenine-induced CKD rats.

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CONFLICT OF INTEREST

None declared.

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