|| Print ISSN: 2589-7837 || Online ISSN: 2581-3935 ||
International Journal of Medical Science and Diagnosis Research (IJMSDR)
Available Online at www.ijmsdr.com
NLM (National Library of Medicine ID: 101738825)
Original Research Article
Volume 4, Issue 5; May: 2020; Page No. 05-08

EFFECT OF SEVELAMER AND CALCIUM ACETATE ON FGF-23 LEVELS IN NON-DIABETIC CKD PATIENTS: AN OBSERVATIONAL STUDY.

Arvind Gupta[1], Upma Narain[2], Saurabh K Shukla[3]
[1]MD, DNB, Professor, Department of Medicine, MLN Medical College, Prayagraj
[2]D.Phil., Senior Microbiologist, Tejas Microdiagnostics, Prayagraj
[3]MD, Resident, Department of Medicine, MLN Medical College, Prayagraj
Conflicts of Interest: Nil
Corresponding author: Upma Narain

Abstract:
Elevated FGF-23 is the earliest and most common manifestation of disordered mineral metabolism in chronic kidney disease. Phosphate binders are routinely prescribed to lower FGF-23 levels and to reduce the risk of morbidity related to imbalance in bio-chemical parameters. This study was designed to compare the efficacy of calcium acetate to sevelamer in reducing FGF-23 levels in patients with chronic kidney disease.
An observational study of 810 patients of chronic kidney disease divided into two groups of 405 each was conducted in SRN Hospital during July 2017 to August 2019. Sevelamer 800 mg and 667 mg calcium acetate were given to group 1 and group 2 respectively in order to compare the efficacy of sevelamer to calcium acetate in reducing the FGF-23 levels in patients with chronic kidney disease. Statistical analysis was performed using descriptive statistics and repeated measure ANOVA-One way by IBM SPSS 24.
A statistically significant change in FGF-23 levels and other parameters like calcium, phosphorus and intact PTH was observed in treatment with both sevelamer as well as calcium acetate. However, the patients who were prescribed sevelamer exhibited with a remarkable tendency to have a greater reduction in mean FGF-23 levels from 0 to 6 months and 6 to 9 months (33.72 ± 8.77 and 2.17 ± 16.98) as compared to those who were prescribed calcium acetate (75.18 ± 0.03 and 178.11 ± 15.80) respectively.
Our study clearly establishes the superiority of sevelamer over calcium acetate in reducing FGF-23 levels and in achieving the target levels of calcium, phosphorus and iPTH clinically and statistically leading us to conclude the possibility of sevelamer being a viable therapeutic alterative in patients of chronic kidney disease.
Keywords: Sevelamer, calcium acetate, FGF-23, chronic kidney disease.

Introduction

Elevated FGF-23 is the earliest and most common manifestation of disordered mineral metabolism in chronic kidney disease (CKD) [1]. In contrast to serum phosphate, FGF-23 levels do not vary substantially within individuals throughout the day, in relation to prandial status or over the course of weeks to months [2]. This is because FGF-23 regulates serum phosphate levels through its endocrine effects on the kidney, gut, and parathyroid glands, FGF-23 is a promising biomarker to detect responses to interventions aimed at lowering phosphate absorption [3].

The effects of phosphate binders on levels of FGF-23 in patients with CKD are not consistent. Several studies suggest that non-calcium based phosphate binders lower FGF-23 levels in this population by 30%– 40% [3-4], whereas calcium-based binders do not [5], this is most likely because calcium is a secondary stimulus for FGF-23 production [6]. Therefore, this study was designed to compare the efficacy of calcium acetate to sevelamer in reducing FGF-23 levels in patients with CKD.

Materials and Methods:

An observational prospective study was undertaken at SRN Hospital, Allahabad from July 2017 to August 2019. All patients of stage 4 and stage 5 with unstable eGFR for the last 6 months, patients whose serum potassium value was >5.0, patients who had potentially reversible and rapidly progressing renal diseases, systemic diseases, severe cardiac or hepatic dysfunction, ankle edema or proteinuria greater than 5 gm/day, glomerulonephritis patients being treated with steroids, non-steroidal anti inflammatory drugs and cytotoxic drugs were excluded from the study. After detailed examination 810 patients of CKD were selected for the study who was regular patients at the nephrology OPD. Serum levels of FGF-23 and other base line investigations were done at the start of the study. These patients were divided into 2 groups of 405 patients each with. Group I being prescribed sevelamer 800 mg and Group II 667 mg of calcium acetate with meals for nine months. Follow-up was done on monthly basis. Same investigations were recorded on 6^{th} month and 9 month respectively. ELISA kit for human FGF-23 (code number EZH FGF-23 32 K) was used to measure FGF-23 levels.

Statistical analysis was performed using descriptive statistics including mean and standard deviation and repeated measure ANOVA-One way for analysing the data.

Results and Discussion:

During the period between July 2017 to August 2019, 810 patients with CKD were registered in Nephrology OPD of Allahabad. These patients were divided into 2 groups of 405 patients each. Group I was prescribed sevelamer 800 mg and Group II was prescribed 667 mg calcium acetate with meals for nine months. The mean age of group 1 patients was 54.8 $\pm$ 2.1 years with males being about 62% and females about 38% while the mean age of group 2 patients was 51.0 $\pm$ 2.1 years with males being about 58% and females about 42%. All the necessary investigations were noted on day 1 (level 1), in the 6th month (level 2) and in the 9 month (level 3).

Table 1(a): Descriptive analysis of the effect of sevelamer and calcium acetate upon FGF-23 levels.

Sr. No.	Time Duration	Sevelamer	Calcium Acetate
		Mean $\pm$ Std. Deviation	Mean $\pm$ Std. Deviation
1	FGF-23 00	640.40 $\pm$ 238.40	608.29 $\pm$ 107.66
	FGF-23 06	607.68 $\pm$ 247.17	533.11 $\pm$ 107.63
	FGF-23 09	423.40 $\pm$ 221.42	430.18 $\pm$ 123.46

Table 1(b): Repeated measure analysis to estimate the impact of sevelamer and calcium acetate upon FGF-23 levels.

Group of Medicines	Source	Time	df	Mean Square	Sig
Sevalmer	FGF-23	0 month vs. 6 month	1	1070.59	.000
		9 month vs. 0 month	1	47089.00	.000
	Error	0 month vs. 6 month	24	9366.250	
		9 month vs. 0 month	24	3628.606	
Calcium Acetate	FGF-23	0 month vs. 6 month	1	5652.03	.000
		9 month vs. 0 month	1	31723.17	.000
	Error	0 month vs. 6 month	26	7270.610	
		9 month vs. 0 month	26	7611.439	

Table 1(a) reveals that sevelamer patients had a higher tendency to have a greater reduction in mean FGF-23 levels from 0 to 6 months and 6 to 9 months (33.72 $\pm$ 8.77 and 2.17 $\pm$ 16.98) than did calcium acetate (75.18 $\pm$ 0.03 and 178.11 $\pm$ 15.80) respectively. A statistically significant change in FGF-23 levels was observed in treatment with both sevelamer as well as calcium acetate as depicted in table 1(b).

Table 2(a): Descriptive analysis of the effect of sevelamer and calcium acetate upon phosphorus levels.

Sr. No.	Time Duration	Sevelamer	Calcium Acetate
		Mean $\pm$ Std. Deviation	Mean $\pm$ Std. Deviation
1	Phosphorus 00	6.03 $\pm$ 1.37	5.63 $\pm$ 1.46
	Phosphorus 06	4.81 $\pm$ 0.76	5.16 $\pm$ 1.53
	Phosphorus 09	3.90 $\pm$ 0.85	4.76 $\pm$ 1.58

Table 2(b): Repeated measure analysis to estimate the impact of sevelamer and calcium acetate upon phosphorus levels.

Group of Medicines	Source	Time	df	Mean Square	Sig
Sevalmer	Phosphorus	0 month vs. 6 month	1	3.42	.000
		9 month vs. 0 month	1	2.13	.269
	Error	0 month vs. 6 month	24	2.681	
		9 month vs. 0 month	24	.510	
Calcium Acetate	Phosphorus	0 month vs. 6 month	1	0.22	.000
		9 month vs. 0 month	1	0.75	.000
	Error	0 month vs. 6 month	26	.243	
		9 month vs. 0 month	26	.486	

Table 2(a) illustrates that sevelamer patients presented with the tendency to have a greater reduction in mean phosphorus levels from 0 to 6 months and 6 to 9 months (1.85 $\pm$ 0.67 and 2.13 $\pm$ 0.52) than did calcium acetate (0.22 $\pm$ 0.10 and 0.75 $\pm$ 0.01) respectively and table 2(b) depicts that calcium acetate and sevelamer brought about a significant change in phosphorus levels in patients put on these compounds.

Table 3(a): Descriptive analysis of the effect of sevelamer and calcium acetate upon calcium levels.

Sr. No.	Time Duration	Sevelamer	Calcium Acetate
		Mean $\pm$ Std. Deviation	Mean $\pm$ Std. Deviation
1	Calcium 00	1.24 $\pm$ 0.21	1.05 $\pm$ 0.13
	Calcium 06	1.13 $\pm$ 0.15	0.96 $\pm$ 0.08
	Calcium 09	1.07 $\pm$0.13	0.91 $\pm$ 0.08

Table 3(b): Repeated measure analysis to estimate the impact of sevelamer and calcium acetate upon calcium levels.

Group of Medicines	Source	Time	df	Mean Square	Sig
Sevalmer	Calcium	0 month vs. 6 month	1	.336	.000
		9 month vs. 0 month	1	.335	.000
	Error	0 month vs. 6 month	24	.016	
		9 month vs. 0 month	24	.012	
Calcium Acetate	Calcium	0 month vs. 6 month	1	.210	.000
		9 month vs. 0 month	1	.250	.000
	Error	0 month vs. 6 month	26	.008	
		9 month vs. 0 month	26	.005	

Table 3(a) shows that sevalmar patients presented a tendency to have a greater reduction in mean calcium levels from 0 to 6 months and 6 to 9 months (0.11 $\pm$ 0.06 and 0.17 $\pm$ 0.08) as compare to the patients who took calcium acetate (0.09 $\pm$ 0.05 and 0.14 $\pm$ 0.05) respectively and table 3(b) illustrates that both the patients who were treated with sevelamer and calcium acetate showed a significant difference in calcium levels.

Table 4(a): Descriptive analysis of the effect of sevelamer and calcium acetate upon iPTH levels.

Sr. No.	Time Duration	Sevelamer	Calcium Acetate
		Mean ± Std. Deviation	Mean ± Std. Deviation
1	Intact PTH 00	241.04 ± 97.25	343.62 ± 199.22
	Intact PTH 06	179.28 ± 79.04	235.11 ± 128.46
	Intact PTH 09	143.04 ± 59.84	299.11 ± 161.44

Table 4(b): Repeated measure analysis to estimate the impact of sevelamer and calcium acetate upon iPTH levels.

Group of Medicines	Source	Time	df	Mean Square	Sig
Sevalmer	iPTH	0 month vs. 6 month	1	3814.29	.000
		9 month vs. 0 month	1	9604.16	.000
	Error	0 month vs. 6 month	24	1258.440	
		9 month vs. 0 month	24	3674.652	
Calcium Acetate	iPTH	0 month vs. 6 month	1	11774.42	.000
		9 month vs. 0 month	1	1427.32	.033
	Error	0 month vs. 6 month	26	4937.846	
		9 month vs. 0 month	26	31326.413	

Table 4(a) depicts that sevelamer patients exhibited a tendency to have a greater reduction in mean iPTH levels from 0 to 6 months and 6 to 9 months (61.76 ± 18.21 and 98.00 ± 37.41) than did calcium acetate (108.51 ± 70.76 and 44.51 ± 37.78) respectively and table 4(b) throws light on patients treated with sevelamer in whom a statistically significant change in iPTH levels was also observed as it was observed on treating with calcium acetate. However, the mean square difference is high in case of sevelamer.

FGF-23 is a regulator of calcium-phosphate metabolism. It is not just a marker of the derangements of calcium-phosphate metabolism in CKD, but rather a relevant factor responsible for the inception of secondary hyperparathyroidism and for cardiovascular morbidity and mortality [7]. In CKD, circulating FGF-23 levels gradually increase with declining renal function such that by the time patients reach end-stage renal disease, FGF-23 levels can be up to 1000-fold above the normal range [8]. The increase in FGF-23 begins at a very early stage of CKD as a physiological compensation to stabilize serum phosphate levels as the number of intact nephrons declines [9]. It is also likely that FGF-23 levels depend on an increased secretion due to an end-organ resistance to the phosphaturic stimulus of FGF-23 because of a deficiency of the necessary Klotho cofactor [10-11].

In the current study we analyzed the levels of FGF-23 along with those of calcium, phosphorus and iPTH in patients in non-diabetic CKD patients.

Serum FGF-23

The current study revealed that sevelamer patients had a higher tendency to have a greater reduction in FGF-23 levels than did calcium acetate. Certain studies compared the effects of specific phosphate binders on FGF-23 levels. In the first study, sevelamer but not calcium acetate lowered FGF-23 levels over a 6 week duration of intervention in CKD stage 3–4 patients with normal serum phosphate levels [12]. The second study randomized 100 hyperphosphatemic stage 4 patients to sevelamer or calcium acetate [13]. Although each intervention lowered serum phosphate, sevelamer but not calcium significantly lowered FGF-23 and significantly improved endothelial function.

Serum Phosphate

In our study mean difference of sevelamer is high i.e. it is more effective than calcium acetate. However, a meta-analysis of 23 studies showed no significant difference in end result of treatment of serum phosphate between sevelamer and calcium acetate [14] while CARE study reported that calcium acetate was found to be more effective than sevelamer hydrochloride for control of serum phosphorus [15].

Serum Calcium

Our results revealed that calcium was significantly lower with sevelamer in comparison to calcium acetate. A meta-analysis of 22 studies and CARE study also reported the same [14-15].

Serum iPTH

We found a greater reduction in mean iPTH levels in the case of sevelamer. However, few studies reported that iPTH was higher for patients treated with sevelamer when compared with calcium acetate while the CARE study that was done did not noticed any significant difference in iPTH levels between the two groups at the end of the study [14-15].

Our study clearly establishes the superiority of sevelamer over calcium acetate in reducing FGF-23 levels and in achieving the target levels of calcium, phosphorus and iPTH clinically and statistically in CKD patients. Hence we conclude that sevelamer could represent a promising therapeutic alternative in comparison to calcium acetate that might improve the quality of life of patients with CKD.

References

1. T. Isakova, P. Wahl, G.S. Vargas, O.M. Gutiérrez, J. Scialla , H. Xie, et al., 'Fibroblast growth factor 23 is elevated before parathyroid hormone and phosphate in chronic kidney disease', Kidney Int, vol. 79, 2011, p. 1370–1378.
2. T. Isakova, H. Xie, A. Barchi-Chung, K. Smith, N. Sowden, M. Epstein, et al., 'Daily variability in mineral metabolites in CKD and effects of

dietary calcium and calcitriol', Clin J Am Soc Nephrol, vol. 7, 2012, p. 820–828.

3. N. Khosla, S. Fettman, H. Gerseny, S.M. Sprague, 'Impact of lanthanum carbonate on FGF-23 in chronic kidney disease stages 3-5 [Abstract]', J Am Soc Nephrol, vol. 23, 2012, p. 312A.

4. G.A. Block, S. Fishbane, M. Rodriguez, G. Smits, S. Shemesh, P.E. Pergola, et al., 'A 12-week, double-blind, placebo-controlled trial of ferric citrate for the treatment of iron deficiency anemia and reduction of serum phosphate in patients with CKD stages 3-5', Am J Kidney Dis, vol. 65, 2014, p. 728–736.

5. T. Radanovic, C.A. Wagner, H. Murer, J. Biber, 'Regulation of intestinal phosphate transport. I. Segmental expression and adaptation to low-P(i) diet of the type IIb Na(+)-P(i) cotransporter in mouse small intestine', Am J Physiol Gastrointest Liver Physiol, vol. 288, 2005, p. G496–G500.

6. M.E. Rodriguez-Ortiz, I. Lopez, J.R. Muñoz-Castañeda, J.M. Martinez-Moreno, A.P. Ramírez, C. Pineda, et al., 'Calcium deficiency reduces circulating levels of FGF-23', J Am Soc Nephrol, vol. 23, 2012, p. 1190–1197.

7. D. Russo, Y. Battaglia, 'Clinical Significant of FGF-23 in Patients with CKD', Int J Nephrol, vol. 2011, 2011, p. 364890.

8. O. Gutierrez, T. Isakova, E. Rhee, A. Shah, J. Holmes, G. Collerone, et al., 'Fibroblast growth factor-23 mitigates hyperphosphatemia but accentuates calcitriol deficiency in chronic kidney disease', J Am Soc Nephrol, vol. 16, no. 7, 2005, p. 2205-2215.

9. D. Fliser, B. Kollerits, U. Neyer, D.P. Ankerst, K. Lhotta, A. Lingenhel, et al., 'Fibroblast Growth Factor 23 (FGF-23) predicts progression of chronic kidney disease: the mild to moderate kidney disease (MMKD) study', J Am Soc Nephrol, vol. 18, no. 9, 2007, p. 2600–2608.

10. Y. Imanishi, M. Inaba, K. Nakatsuka, K. Nagasue, S. Okuno, A. Yoshihara, et al., 'FGF-23 in patients with end-stage renal disease on hemodialysis', Kidney Int, vol. 65, no. 5, 2004, p. 1943-1946.

11. N. Koh, T. Fujimori, S. Nishiguchi, A. Tamori, S. Shiomi, T. Nakatani, et al., 'Severely reduced production of klotho in human chronic renal failure kidney', Biochem Biophys Res Commun, vol. 280, no. 4, 2001, p. 1015-1020.

12. R.B. Oliveira, A.L. Cancela, F.G. Graciolli, L.M. Dos Reis, S.A. Draibe, L. Cuppari, et al., 'Early control of PTH and FGF-23 in normophosphatemic CKD patients: a new target in CKD-MBD therapy?', Clin J Am Soc Nephrol, vol. 5, 2010, p. 286–291.

13. M.I. Yilmaz, A. Sonmez, M. Saglam, H. Yaman, S. Kilic, T. Eyileten, et al., 'Comparison of calcium acetate and sevelamer on vascular function and fibroblast growth factor 23 in CKD patients: a randomized clinical trial', Am J Kidney Dis, vol. 59, no. 2, 2012, p. 177-185.

14. L. Patel, L.M. Bernard, G.J. Elder, 'Sevalamer Versus Calcium-Based Binders for Treatment of Hyperphosphatemia in CKD: A Meta-Analysis of Randomized Controlled Trials', Clin J Am Soc Nephrol, vol. 11, 2016, p. 232-244.

15. W.Y. Qunibi, C.R. Nolan, 'Treatment of hyperphosphatemia in patients with chronic kidney disease on maintenance hemodialysis: Results of the CARE study', Kidney Int, Suppl, vol. 90, 2004, p. S33-S38.