Long-term Use of Calcium-based Phosphate Binders Lower Serum Fetuin-A Levels but not Sevelamer

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Introduction

Fetuin-A, a circulating inhibitor of vascular calcification, is important to stabilize and clear amorphous mineral precursors and acts as an efficient barrier to slow down vascular mineralization. Short-term sevelamer treatment (8 weeks) has shown to increase serum fetuin-A levels in CKD and chronic hemodialysis patients. However, research data about long-term effect of sevelamer on serum fetuin-A level is currently unavailable.

Aim

This study is aimed to study long-term impact of sevelamer on circulating fetuin-A level, compairing with calcium-based phosphate binder.

Methods

In this post-hoc study of a multi-center randomized controlled trial, we analyzed serum fetuin-A and other biochemical factors (Ca, P, i-PTH, alkaline phospatase, hsCRP, LDL-C) in 50 hemodialysis patients, who completed a 48-week, open-Label, controlled randomized parallel-group study, using either sevelamar or calcium carbonate as phosphate-binders (Fig. 1). The baseline clinical data between these two groups was shown in Table.1.This is a per-protocol analysis including only the population who completed 48-week treatment of either agent. Statistical analyses were performed using the IBM SPSS statistics 20.

Results

- Fifty patients completed the 48-week treatment, including 23 patients who received sevelamer and 27 patients who received calcium carbonate.
- The baseline serum fetuin-A level had a positive correlation with serum albumin level (β =2.982, P = 0.005)(Table 2).
- After 48-week sevelamer treatment, there were significantly higher calcium, lower LDL-C and insignificant reduction of serum fetuin-A level (179.81 ±116.47 vs.242.95 ±114.49 ug/mL, P=0.074). In the calcium carbonate group, there were significantly higher serum calcium, lower phosphate, lower iPTH and lower fetuin-A level (182.90 ± 63.38 vs.236.73 ± 97.97 ug/mL, P =0.010) (Table 3).
- The change of biochemical parameters before and after treatment was shown in Table 4.
- Multivariate analysis showed the decrease of serum fetuin-A was mainly associated with the change of serum calcium level (β= -0.377, P=0.024), but not related to the use of sevelamer, or change of either serum phosphate or hsCRP levels (Table 5).

Limitations

- The number of patients studied was small (n=50).
- We did not measure intermediate fetuin-A level at week 24.
- We did not measure vitamin D level.

Discussions

- Fetuin-A binds to serum calcium and phosphate, forming small calciprotein particles that are presumably removed through the reticuloendothelial system and normal kidney.
- Serum fetuin-A levels are lower in CKD patients and hemodialysis patients. It is associated with higher cardiovascular calcification and mortality
- Previously, a short-term (8 weeks) study in CKD stage 4 patients and another short-term (8 weeks) study in chronic HD patients both showed sevelamer increased the serum fetuin-A levels. However, our study did not confirm this direct uplifting of fetuin-A by sevelemar in HD patients. We found higher serum calcium levels are pivotal to lower serum fetuin-A levels.

Conclusions

- After 48-wk phosphate binder use in maintenance HD patients, only those used calcium carbonate had significantly reduced serum fetuin-A levels but not in those taking sevelamer.
- The most important factor influencing serum fetuin-A level was serum calcium level. The fetuin-A level was not correlated with the change of either serum phosphate level or the use of sevelamer.

Figure 1. The flow chart of enrolled patients

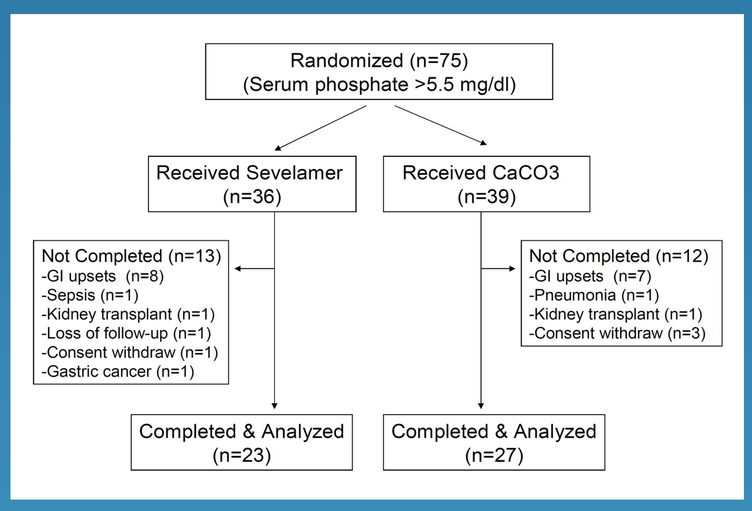

Table 1. Baseline characteristics and parameters between two groups

	Sevelamer (n=23)	Calcium Carbonate (n=27)	*P*
Age (yr)	59.61 ± 8.16	56.96 ± 7.72	0.248
Gender (male)	11 (47.83%)	18 (66.67%)	0.149
Hemodialysis (yr)	7.48 ± 3.45	7.33 ± 5.21	0.907
DM (no)	9 (39.13%)	8 (29.63%)	0.557
Use of vitamin D (no)	9 (39.13%)	13(48.14%)	0.577
Use of vitamin D (months)	77	81	0.775
LCB (no)	7 (30.43%)	6 (22.22%)	0.537
Statin (no)	7 (30.43%)	5 (18.52%)	0.305
Anti-hypertension drug (no)	16 (69.56%)	20 (74.07%)	0.761
Ca (mg/dL)	9.37 ± 0.66	9.37 ± 0.73	0.986
P (mg/dL)	6.54 ± 0.91	7.22 ± 0.98	0.015*
iPTH (pg/mL)	354.70 (332.70)	320.90 (371.8)	0.633
ALK-P (IU/L)	82.17 ± 32.71	65.67 ± 23.70	0.061
HsCRP (mg/L)	5.71 ± 9.26	4.15 ± 3.65	0.454
Hct (%)	33.10 ± 3.87	32.49 ± 3.11	0.549
Albumin (g/L)	39.92 ± 3.13	39.81 ± 2.86	0.866
LDL-C (mg/dL)	108.96 ± 30.10	112.93 ± 33.46	0.661
Fetuin-A (ug/mL)	242.95 ± 114.49	236.73 ± 97.97	0.839

Data are mean ± standard deviation or median (interquartile range, IQR)
LCB: low calcium bath (Ca 1.25 mmol/L)
P < 0.05*

Table 2. Correlation of baseline serum fetuin-A levels with other parameters before treatment

	Fetuin-A (ug/mL)	
	Univariate *β* (*P*)	Multivariate *β* (*P*)
Age (yr)	-0.079 (0.585)	-0.061 (0.655)
HD duration (yr)	-0.215 (0.133)	-0.155 (0.268)
DM or not	-0.072 (0.620)	-0.036 (0.806)
HsCRP (mg/L)	-0.191 (0.184)	-1.009 (0.318)
Albumin (g/L)	**0.436 (0.002*)**	**2.982 (0.005*)**

P < 0.05*

Table 3. Comparison of parameters before and after treatment in each group

	Sevelamer (n=23)			Calcium Carbonate (n=27)		
	BT	AT	*P*	BT	AT	*P*
Ca (mg/dL)	**9.37 ± 0.66**	**9.63 ±0.80**	**0.038***	**9.37 ± 0.73**	**10.17 ± 0.90**	**0.000***
P (mg/dL)	**6.54 ± 0.91**	**5.07 ± 0.85**	**0.000***	**7.22 ± 0.98**	**5.70 ± 1.01**	**0.000***
iPTH (pg/mL)	354.70 (332.70)	329.60 (319.80)	0.903	**320.90 (371.8)**	**165.20 (405.6)**	**0.001***
ALK-P (IU/L)	**82.17 ± 32.71**	**112.43 ± 43.21**	**0.004***	65.67 ± 23.70	64.41 ± 23.13	0.609
HsCRP (mg/L)	5.71 ± 9.26	8.16 ± 25.37	0.652	4.15 ± 3.65	4.62 ± 5.44	0.548
Hct (%)	33.10 ± 3.87	32.80 ± 3.72	0.728	32.49 ± 3.11	32.49 ± 4.58	0.996
Albumin (g/L)	39.92 ± 3.13	39.96 ± 3.02	1.000	39.81 ± 2.86	40.78 ± 2.95	0.062
LDL-C (mg/dL)	**108.96 ± 30.10**	**63.91 ± 20.55**	**0.000***	112.93 ± 33.46	105.19 ± 30.93	0.157
Fetuin-A (ug/mL)	**242.95 ± 114.49**	**179.81 ± 116.47**	**0.074**	**236.73 ± 97.97**	**182.90 ± 63.38**	**0.010***

BT: before treatment; AT: after treatment
Data are mean ± standard deviation or median (interquartile range, IQR)
P < 0.05*

Table 4. Comparison of the changes of parameters before and after treatment between two groups

	Sevelamer (n=23)	Calcium Carbonate (n=27)	*P*
Δ Ca (mg/dL)	0.26 ± 0.55	0.80 ± 0.93	0.015*
Δ P (mg/dL)	-1.47 ± 0.98	-1.53 ± 1.27	0.871
Δ iPTH (pg/mL)	**12.10 (216.60)**	**-137.10 (255.70)**	**0.026***
Δ ALK-P (IU/L)	**30.26 ± 45.78**	**-2.26 ± 22.69**	**0.004***
Δ HsCRP (mg/L)	2.45 ± 25.73	0.48 ± 4.08	0.719
Δ Hct (%)	-0.30 ± 4.00	-0.00 ± 3.39	0.785
Δ Albumin (g/L)	0.00 ± 2.72	0.82 ± 2.31	0.241
Δ LDL-C (mg/dL)	**-45.04 ± 28.31**	**-7.74 ± 27.59**	**0.000***
Δ Fetuin-A (ug/mL)	-63.13 ± 161.24	-53.82 ± 100.13	0.812

Δ Ca: the change in serum calcium
Data are mean ± standard deviation or median (interquartile range, IQR)
P < 0.05*

Table 5. Analysis of Δ Fetuin-A and changes of related parameters

	Δ Fetuin-A (ug/mL)	
	Univariate *β* (*P*)	Multivariate *β* (*P*)
Sevelamer or not	-0.036 (0.804)	-0.141 (0.353)
Vitamin D or not	-0.038 (0.792)	0.012 (0.936)
LCB or not	0.103 (0.477)	0.104 (0.483)
Δ P (mg/dL)	0.054 (0.711)	-0.008 (0.958)
Δ Ca (mg/dL)	**-0.295 (0.038*)**	**-0.377 (0.024*)**
Δ hsCRP (mg/L)	-0.152 (0.291)	-0.157 (0.289)

Δ Fetuin-A: the change in serum Fetuin-A
LCB: low calcium bath (Ca 1.25 mmol/L)
P < 0.05*

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