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The Effect of Early Targeting Fibroblast Growth Factor 23 and Microalbuminuria by Using Phosphate Binders in Diabetic Nephropathy Deterioration

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ABSTRACT

Background: *Diabetic nephropathy consists of major pathology for deterioration of chronic kidney disease. Microalbuminuria and fibroblast growth factor 23 (FGF23) reflects an early marker for kidney disease deterioration. Kidney Disease Improving Global Outcomes (KDIGO) restrict the use of phosphate binder (PB) for hyperphosphatemia that manifested at late stages only.* ***Objective:*** *To study the effect of early treatments of PBs in normophosphatemic diabetic nephropathic patients.* ***Material and methods:*** *A Randomized control trial was conducted during the period December 2016 to October 2017, including 75 patients with chronic kidney disease. Patients were assigned into three groups according to the type of treatment. The primary end points were the effects of intervention on serum fibroblast growth factor and urinary albumin creatinine ratio.* ***Results:*** *Both phosphate binders significantly reduced serum phosphate at similar extent with significant reduction in serum fibroblast growth factor 23. Sevelamer showed pleiotropic effect beyond phosphate control that reduces HBA1c and plasma glucose level with antiproteinuric effect. In both treatment arms, serum creatinine was reduced but the differences did not reach the statistical significance ($p>0.05$).* ***Conclusion:*** *Thus, early intervention with calcium carbonate and sevelamer reduce disease progression by earlier control of FGF23 level. Maximal beneficial effect was noticed by early use of sevelamer HCl supported by reduction in UACR and more glycemic control in early stage of diabetic nephropathy.*

Keywords: Diabetic nephropathy, FGF23, UACR, Phosphate binders

Abbreviations: eGFR: Estimated Glomerular Filtration Rate; MDRD: Modification of Diet in Renal Disease; UACR: Urine Albumin-to-Creatinine Ratio; AGEs: Advanced Glycation End Products; RAAS: Renin-Angiotensin-Aldosterone System

INTRODUCTION

Chronic kidney disease (CKD) is considered the most common cause of mortality in United States with annual death rate of about 2% [1]. The prevalence of this disease reached to about 13% with most occurrence rate at stage 3 [2]. Diabetic nephropathy is considered the major pathology for development of renal failure [3]. Very limited data was found about prevalence rate of CKD in Iraqi population. However, about 30% of population had diabetic nephropathy [4]. In 2012, Kidney Disease Improving Global Outcomes (KDIGO) classified CKD based on the etiology, presence of albuminuria and glomerular filtration level [5]. The presence of protein in urine was associated with an increase in the occurrence of CKD and early initiate renal dialysis [6]. Two methods were found for evaluation of albuminuria, the first depend on 24 hours urine collection which is considered the golden test, but it was time consuming and difficult to use, while the second test was based on measurement of untimed urinary albumin to creatinine ratio (UACR) that best reflect the former test [7]. Hyperglycemia induces the pathogenesis of nephropathy through stimulation of hemodynamic and metabolic ways to initiate the nephron damage [8]. These negative implications were attributed to the reaction of high glucose level with proteins that form abnormal advance glycation product [9]. These products

react with its receptor at glomeruli to negatively affect the glomerular epithelial integrity and result in formation of proteinuria [10]. The proposed mechanism for this lesion was based on interaction of AGE and release of several reactive oxygen species that result in cellular damage [11]. Once micro-albuminuria is developed, it will initiate and progress in worsening of the disease [12]. CKD manifests several complications, one of them was referred to chronic kidney disease-mineral bone disorder (CKD-MBD) that was associated with abnormal bone and soft tissue calcification [1]. This complication is manifested by elevation in serum phosphate level together with hyperparathyroidism and elevation of serum fibroblast growth factor 23(FGF23) which is the hallmark of this disease [13]. FGF23 activates with dietary phosphate intake and results in regulation of serum phosphate level [14]. Lot of studies considers FGF23 as a good marker that reflects early CKD worsening and dialysis initiation [15-17]. Abnormal FGF23 elevation was developed earlier to elevate PTH and serum phosphate that is associated with bad CKD prognosis [18]. KDIGO CKD-MBD states that phosphate restriction by diet should be used in early stage CKD, while the use of phosphate binder is only authorized for patients with hyperphosphatemia [5]. Thus, this study was conducted to evaluate the effect of aggressive control on FGF23 by early use of phosphate binder in normophosphatemic patients. Kidney disease deterioration is the most common cause of CKD and diabetic nephropathy.

PATIENTS AND METHODS

A total of 75 patients were diagnosed with diabetic nephropathy, where they were randomly assigned into three groups to receive either sevelamer HCl, 800 mg with each meal, calcium carbonate, 600 mg with each meal or placebo at Babylon Murjan Hospital, Babil province, Iraq during the period December 2016 to October 2017. Adult patients of both genders were enrolled in this study. Patient was excluded from the study if he/she had hypo or hyperphosphatemia, change in vitamin D or RAAS blocker, history of hospitalization within the last four weeks, inflammatory bowel disease, liver disease, kidney transplant, polycystic kidney, malnutrition, parathyroid disease. Additionally, pregnant women, patients currently on anti-convulsant or antiarrhythmic agent, those who were allergic to treatment, had progressive microalbuminuria and those patients with calcium phosphate product $p \geq 55$ mg^2/dl^2 all were excluded. Diabetes was confirmed according to adenosine deaminase, with duration of more than 5 years in patients with type I diabetes and at time of diagnosis in those with type II diabetes mellitus. Specialist nephrologist confirmed diabetic nephropathy. Venous blood sample of 5 ml was collected. In addition to routine laboratory investigations, HBA1c, fasting blood glucose, serological and biochemical tests were performed. First voiding urination was tested for microalbuminuria. FGF23 was assayed using sandwich ELISA technique by aid of ready-made human FGF23 ELISA kit. Serum glucose, phosphate, calcium, urea, and creatinine were all investigated. Urinary albumin creatinine ratio, and urine creatinine was assayed. Glomerular filtration rate was calculated using eGFR MDRD equation [19]. Data analysis was performed using the statistical package for social sciences (SPSS) version 24. Statistics were presented as mean, standard error of mean (SEM) and range and compared using paired-t-test for differences within each group and analysis of variance (ANOVA) with LSD (least significant difference) post-hoc testing to compare the mean levels of the studied parameters among the three groups before and three months after treatment. Level of significance was set at p=0.05.

RESULTS

After initiation of the study, some of the patients were missed to follow up, and the net number of participants who completed the study was 19, 20 and 22 in the calcium carbonate, sevelamer and placebo groups, respectively. The baseline characteristics of the studied groups are shown in Table 1, where no statistically significant differences had been reported among the studied groups in these variables, (in all comparison, p>0.05).

Table 1 Baseline characteristics of the studied groups

Variable	Group			P-value
	Ca Carbonate (n=19)	Sevelamer HCl (n=20)	Placebo (n=22)	
Age in year, (mean (SD))	57.4 (7.6)	62.7 (8.4)	62.7 (11.4)	0.71
Male (n (%))	13 (68.4)	11 (55.0)	19 (86.4)	0.11
BMI (kg/m^2), mean (SD)	28.89 (1.95)	28.90 (1.80)	28.63 (1.83)	0.63
Diabetes Type I n (%)	4 (21.1)	3 (15.0)	7 (31.8)	0.42
Diabetes Type II n (%)	15 (78.9)	17 (85.0)	15 (68.2)	0.64
Systolic blood pressure (mmHg) (mean (SD))	128.7 (5.8)	129.6 (6.3)	130.5 (6.4)	0.14
Diastolic blood pressure mmHg (mean (SD))	88.7 (9.3)	89.1 (7.2)	88.6 (6.3)	0.53

The serum urea level was elevated in all the three groups. However, the differences were statistically insignificant, neither within nor between groups ($p>0.05$). In both calcium carbonate and sevelamer groups' patient had reduction in serum creatinine level by 4% and 6%, respectively, compared to its baseline level, and had elevation in eGFR MDRD level by 4.1% and 4%, respectively. However, these changes were statistically insignificant ($p>0.05$). Regarding the UACR, it was significantly reduced at post treatment compared to its baseline values, and the mean difference in UACR in this group was significantly different than that in the other two groups: calcium carbonate and placebo (Table 2).

Table 2 Comparison of the studied groups in the pre- and post-treatment levels of blood urea, serum creatinine, UACR and eGFR MDRD

Parameters		Group						P-value between groups
		Ca Carbonate group (n=19)		Sevelamer HCl group (n=20)		Placebo (n=22)		
		mean	SE	mean	SE	mean	SE	
Blood urea (mg/dL)	Baseline	58.18	1.54	63.9	6.93	63.09	2.68	0.62
	Post-treatment	69.06	5.98	69.13	7.27	65.57	2.25	0.86
	mean difference	10.88	6.1	5.22	8.28	2.48	1.85	0.59
	Percentage change	19.80%	11.40%	15.40%	10.30%	5.50%	2.70%	0.49
P-value within group		0.09	-	0.54	-	0.19	-	-
serum creatinine (mg/dL)	Baseline	1.89	0.09	1.74	0.15	1.83	0.18	0.77
	Post-treatment	1.81	0.1	1.61	0.14	1.88	0.16	0.36
	Mean difference*	-0.08	0.05	-0.13	0.09	0.05	0.03	0.1
	Percentage change	-4%	3%	-6%	4%	2.70%	1.60%	0.21
P-value within group		0.144	-	0.13	-	0.44	-	-
UACR	Baseline	9.67	1.06	9.14	0.88	9.95	0.88	0.82
	Post-treatment	10.06	1.05	8.14	0.98	10.02	0.88	0.28
	mean difference	0.39	0.48	-1	0.46	0.07	0.04	0.03
	Percentage change	8.40%	9.20%	13.00%	4.10%	1.00%	0.40%	0.03
P-value within group		0.43	-	0.045	-	0.12	-	-
eGFR MDRD (ml/min)	Baseline	37.62	2.23	44.18	4	46.77	4.3	0.21
	Post treatment	38.75	2.08	45.28	3.86	45.24	3.67	0.31
	mean difference	1.17	0.73	1.06	0.79	-1.53	1.46	0.41
	Percentage change	4.10%	2.50%	4.00%	2.60%	1.50%	5.00%	0.85
P-value within group		0.13	-	0.2	-	0.54	-	-

A significant reduction was observed in FBG and HBA1c in sevelamer treated patients only compared to calcium carbonate and placebo groups. In the Ca carbonate group, a significant increase in the level of serum calcium was observed. On the other hand, a decrease in serum PO_4 and a significant increase in serum calcium and phosphorus (Ca × PO_4) at post treatment compared to baseline levels was observed, ($p<0.05$). In sevelamer HCl group, no significant change in serum calcium was seen ($p>0.05$). A significant reduction in serum PO_4 and insignificant change in Ca × PO_4, ($p>0.05$), was observed at post-treatment compared to baseline levels (Table 3).

Table 3 Pre and post-treatment levels of FBG, HBA1c, serum calcium, Serum PO_4, serum Ca × PO_4 product and FGF23 of the studied groups

Parameters		Ca Carbonate (n=19)		Sevelamer HCl (n=20)		Placebo (n=22)		P-value between groups
		Mean	SE	Mean	SE	Mean	SE	
FBG (mg/dL)	Baseline	154.05	8.47	147.6	8.86	146.77	8.95	0.82
	Post	149.74	8.34	133.4	5.86	150.36	7.26	0.18
	mean difference	-4.32	4.57	-14.2	4.45	3.59	5.06	0.03
	Percentage change	2.10%	2.90%	7.00%	3.20%	4.40%	2.90%	0.03
P-value within group		0.36	-	0.005	-	0.49	-	-

HBA1c (%)	Baseline	7.06	0.07	7.07	0.08	7.03	0.08	0.92
	Post	7.05	0.07	6.58	0.08	7.09	0.06	<0.001
	mean difference	-0.01	0.08	-0.49	0.06	0.06	0.05	<0.001
	Percentage change	0.10%	1.10%	6.90%	0.90%	1.00%	0.80%	<0.001
P-value within group		0.85	-	<0.001	-	0.25	-	-
Serum Ca (mg/dL)	Baseline	10.6	0.12	10.73	0.25	10.15	0.17	0.07
	Post	13.21	0.36	11.4	0.29	10.21	0.18	<0.001
	mean difference	2.61	0.33	0.68	0.39	0.07	0.08	<0.001
	Percentage change	24.70%	3.00%	7.40%	3.50%	0.70%	0.80%	<0.001
P-value within group		<0.001	-	0.097	-	0.42	-	-
Serum PO_4 (mg/dL)	Baseline	3.92	0.12	3.83	0.12	3.88	0.09	0.84
	Post	3.59	0.1	3.29	0.11	3.96	0.08	<0.001
	mean difference	-0.33	0.12	-0.54	0.1	0.08	0.07	<0.001
	Percentage change	7.00%	3.80%	13.30%	2.50%	2.50%	2.10%	<0.001
P-value within group		0.015	-	<0.001	-	0.27	-	-
Serum Ca × PO_4	Baseline	41.55	1.38	41.36	1.92	39.43	1.21	0.54
	Post	47.44	1.93	37.73	1.82	40.51	1.28	<0.001
	mean difference	5.89	2.05	-3.63	2.11	1.08	0.79	0.001
	Percentage change	16.40%	6.00%	6.40%	4.60%	3.20%	2.30%	<0.001
P-value within group		0.01	-	0.1	-	0.19	-	-
Serum FGF23	Baseline	174.62	7.97	166.1	9.82	148.07	9.64	0.12
	Post	140.38	3.62	120.35	5.41	160.76	4.96	<0.001
	mean difference	34.24	8.06	45.74	7.69	12.7	8.54	<0.001
	Percentage change	19.60%	6.20%	27.50%	4.90%	8.60%	8.40%	<0.001
P-value within group		<0.001	-	<0.001	-	0.15	-	-

The multiple comparison showed significant larger change in serum calcium in calcium carbonate group than sevelamer and placebo group ($p<0.05$). However, the change in serum phosphate was significantly larger in both treatment groups than that in placebo group ($p<0.05$), with insignificant difference between treatment groups, ($p>0.05$). The change in Ca × PO_4 was significantly larger in both treatment groups than that in placebo group ($p<0.05$), and it was also significantly larger in calcium carbonate group than that of sevelamer group (Table 4).

Table 4 Post hoc tests (LSD) for the multiple comparisons of mean difference in FBG, HBA1c, serum calcium, serum PO_4 and serum Ca × PO_4 product

Parameters	Group	Mean difference	Multiple comparison (P-value)		
			P1	P2	P3
FBG	Ca Carbonate	4.32	0.15	0.24	0.009
	Sevelamer HCl	14.2			
	Placebo	3.59			
HBA1c	Ca Carbonate	0.02	<0.001	0.4	<0.001
	Sevelamer HCl	0.49			
	Placebo	0.06			
Serum Calcium	Ca Carbonate	2.61	<0.001	<0.001	0.13
	Sevelamer HCl	0.68			
	Placebo	0.07			
Serum PO_4	Ca Carbonate	0.33	0.16	0.005	<0.001
	Sevelamer HCl	0.54			
	Placebo	0.08			
Serum Ca × PO_4	Ca Carbonate	5.89	<0.001	0.05	0.05
	Sevelamer HCl	3.63			
	Placebo	1.08			
P1: Ca Carbonate vs. Sevelamer HCl; P2: Ca Carbonate vs. Placebo; P3: Sevelamer HCl vs. Placebo					

The Serum FGF23 values were significantly reduced than their baseline levels in calcium carbonate group from 174.62 (± 7.97) pg/mL at baseline to 140.38 (± 3.62) pg/mL post-treatment ($p<0.001$), and in sevelamer group reduced from

166.10 (± 9.82) pg/mL at baseline to 120.35 (± 5.41) pg/mL post treatment, conversely it was elevated in placebo group, 148.07 (± 9.64) pg/mL to 160.76 (± 4.96) pg/mL. This change in placebo group was insignificant ($p>0.05$). The differences between groups were statistically significant at post-treatment mean levels of FGF23, mean difference and percentage change ($p<0.001$).

DISCUSSION

This randomized trial has shown that early use of phosphate binders reduced kidney disease deterioration supported by earlier reduction in serum phosphate and FGF23 in both sevelamer and calcium carbonate group. Also, this study has shown that beyond earlier control of FGF23 sevelamer treatment significantly reduced the level of microalbuminuria due to significant reduction in UACR and thus provides an earlier protection against the progressive nature of diabetic nephropathy. These beneficial effects were purely attributed to the treatment intervention as patient's demography have been similar in baseline characteristics. Two studies have agreed with these results in term of early reduction in serum FGF23 in both sevelamer and calcium-based binders [20,21]. This study used the lowest recommended doses for treatment of hyperphosphatemia as stated by KDIGO CKD-MBD 2017 as the patients enrolled in this trial were normophosphatemic and not eligible to phosphate binding strategies. Also, these doses were used to avoid hypophosphatemia. This trial showed that both treatments reduce serum phosphate to similar extent that allowed the trial to equivalently use the dose from each type of phosphate binder. The present trial has shown that calcium carbonate treated patients significantly increase serum calcium level and in turn significantly raise $Ca \times PO_4$ product. The results agreed with other study that used calcium carbonate dosage of 1500 mg, elemental calcium significantly increase serum calcium [22]. This significant increase may be attributed to the calcium content in the calcium carbonate drug [23]. Although sevelamer treated patients also increase calcium level in post-treated patients. However, it does not reach to significant level and this may be explained as a reduction in phosphate absorption from GIT, but sevelamer will increase the available calcium in GIT to be absorbed [24]. Sevelamer treated group have shown more control on glycemic status supported by reduction in HBA1c and FBG compared to other two groups and this, in turn may provide early protection against diabetic nephropathy progression. One of the possible explanation was that sevelamer restrict AGE product absorption from GIT that attributed to sevelamer structure [25]. Another explanation is due to local effect of sevelamer on bile acid to carry it to farthest part and in turn stimulate GLP1 and enhance glucose metabolism [26,27]. This earlier and aggressive glycemic control could also explain how sevelamer reduce microalbuminuria by significant reduction in UACR and provide further kidney protection. An animal study had agreed with these results stating that sevelamer reduce proteinuria in uremic rats [28].

CONCLUSION

Both phosphate binders reduce serum phosphate level and in turn, significantly reduce FGF23 that may provide a way for early halt kidney disease deterioration and reduce the progression of its complication CKD-MBD. None of the treatment arm produce a significant change in serum urea, creatinine nor eGFR level. This may explain that the beneficial effects of the early use of phosphate binder may be attributed to eGFR level. However, both phosphate binders treated groups had a decrease in serum creatinine and increase in eGFR level but not to a significant level that may emerge a need for further long-term evaluation of these markers.

DECLARATIONS

Conflict of Interest

The authors have disclosed no conflict of interest, financial or otherwise.

Ethics and Consent to Participate

Study protocol was approved by the Ethical Committee of the Faculty of Pharmacy, University of Kufa, agreement certificate No. (561/13/2/2017). Ethical approval from Murjan Medical City and Babylon Research and Development Department with certificate No. (1175/1/12/2016). Signed informed consent of each participant patient was obtained and all ethical issues and patients' rights were in accordance with the ethical standards of the responsible ethical committee and with the Helsinki Declaration of 1975, as revised in 2000.

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