The role of clinical pharmacy services in achieving treatment targets in Iranian haemodialysis patients

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INTRODUCTION The number of patients suffering from chronic kidney disease (CKD) is increasing worldwide. Hyperphosphataemia and high serum calcium (Ca) and phosphorus (P) product contribute to the substantial increase in cardiovascular events in CKD patients. Although reports of CKD complications in Iranian haemodialysis (HD) patients are comparable to data from other developed countries, management of these complications has failed to meet generally accepted targets. This study evaluated the impact of clinical pharmacy services in the management of complications in HD patients.

METHODS During a six-month prospective study, clinical pharmacists conducted medical visits in the HD ward and adjusted the patients' medications according to their laboratory findings.

RESULTS Serum Ca concentration was increased in hypocalcaemia patients and decreased in hypercalcaemia patients until it reached the optimal range in both groups. A decline in serum P level was noted in hyperphosphataemia patients, although it did not reach the target range. The Ca × P product decreased in patients with Ca × P > 55 mg^2/dL^2. Although it did not reach the goal, there was an increase and decrease in serum intact parathyroid hormone (iPTH) concentration in suboptimal and supraoptimal range patients, respectively. Serum Ca, P and iPTH levels did not change in patients with optimal values at the initiation of the study. Haemoglobin concentration increased in anaemic patients and serum ferritin reached target values in all patients. Total cholesterol, low-density lipoprotein cholesterol and triglycerides decreased to near-optimal values in dyslipidaemia patients.

CONCLUSION This study showed that clinical pharmacy services at the HD centre can improve the management of complications in CKD patients.

Keywords: anaemia, dyslipidaemia, haemodialysis, hyperparathyroidism, NKF-K/DOQI guidelines
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INTRODUCTION

The number of patients suffering from chronic kidney disease (CKD) and end-stage renal disease (ESRD) is increasing worldwide. In Iran, the prevalence/incidence of ESRD increased from 238/49.9 per million population (pmp) in 2000 to 357/63.8 pmp in 2006.[1,2] The main complications of CKD include bone metabolism disturbances (hyperphosphataemia, high serum calcium [Ca] × phosphorus [P] product and secondary hyperparathyroidism), anaemia (low serum haemoglobin [Hb] and ferritin concentrations, low transferrin saturation [TSAT]) and dyslipidaemia. Hyperphosphataemia and high serum Ca × P product contribute to a substantial increase in cardiovascular events in the CKD population.[3] A report on CKD complications of haemodialysis (HD) patients in Iran has shown that although the results were comparable to data from developed countries,[4,6] management of these complications failed to meet the generally accepted targets set by the National kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI).[5] Based on the report of Mahdavi-Mazdeh et al, only 1.8% of HD patients achieved all four target levels for bone metabolism, intact parathyroid hormone (iPTH) concentration, Hb and ferritin.[4] The unavailability of some phosphate binder agents and active vitamin D products were cited as some of the reasons for these results.

In Iran, all patients have access to calcium carbonate as phosphate binder, calcitriol as active vitamin D product, α-erythropoietin as haematopoietic agent and intravenous iron hydroxide in sucrose complex to replenish iron stores. Other medications for management of hyperphosphataemia and secondary hyperparathyroidism control (e.g. sevelamer, paricalcitol or cinacalcet) or haematopoietic agents (e.g. darbepoetin) are not covered by governmental insurance due to budget limitations, and are therefore rarely used by our patients; however, we postulated that clinical pharmacy services could improve the use of available medications in HD patients in order to reach the target haematologic, bone and lipid metabolism goals in these patients. To date, none of the HD centres in Iran have benefitted from clinical pharmacy services. This study was designed to assess the impact of clinical pharmacy services on the management of secondary complications in patients who were on maintenance HD, including bone metabolism disorders, anaemia and dyslipidaemia.

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METHODS

During a six-month prospective study period, patients on maintenance HD at our treatment centre were managed by clinical pharmacists participating in medical team rounds. All patients were evaluated for bone metabolism parameters (corrected serum Ca, P and iPTH concentrations and Ca × P product), anaemia parameters (serum Hb and ferritin concentrations and TSAT) and serum lipid profile (total cholesterol, low-density lipoprotein [LDL] cholesterol, high-density lipoprotein [HDL] cholesterol and triglyceride [TG] levels) at the beginning of the study and periodically thereafter. Assessments of serum Ca and P concentrations and complete blood counts were routinely performed monthly in stable patients, and weekly or biweekly upon modifications in the medications. Serum iPTH and ferritin concentrations, TSAT and lipid profile were evaluated every three months in stable subjects, and monthly in patients whose drugs were dose-adjusted. During the six months, clinical pharmacists reviewed related medications, including phosphate binders (calcium carbonate, sevelamer and aluminum hydroxide), calcitriol, erythropoietin, intravenous iron sucrose and hMG-CoA reductase inhibitors, and proposed to physicians to adjust the dosage of these drugs according to laboratory data results, availability and cost for each patient.

Control of HD complications was performed according to NKF-K/DOQI guidelines.[5] Dietary phosphate restriction and calcium carbonate (generic brands) were used to control serum Ca and P concentrations and Ca × P product. In addition, calcitriol (generic brands) was used to suppress secondary hyperparathyroidism, while parenteral erythropoietin (Pooyesh-Daru, Tehran, Iran) and iron sucrose (Venofer, Viofer Inc, St Gallan, Switzerland) were used to manage anaemia. Data was analysed using the Statistical Package for the Social Sciences version 13 (SPSS Inc, Chicago, IL, USA). Median (range) and frequency (percentage) were reported for continuous and categorical characteristics, respectively. Comparisons of laboratory data were conducted in a subset of patients defined by the NKF-K/DOQI guidelines.[5] Wilcoxon signed rank test was used to detect significant changes in initial and final laboratory data. Descriptive tests were used to report and compare the percentage of patients in each subset of patients. A p-value < 0.05 was considered to be statistically significant.

RESULTS

A total of 86 patients (55 males and 31 females) with a median age of 56 (22–84) years who underwent maintenance HD at our centre for a median duration of 39 (range 1–267) months completed the study. All the patients received three dialysis sessions per week, each session lasting about four hours. All dialysis cycles were performed using polysulfone dialysers, and the dialysate solutions contained 1.25 mmol/L of calcium with bicarbonate buffer. The median values of bone metabolism parameters (serum Ca, P and iPTH concentrations and Ca × P product) with the percentage of patients whose serum Ca was < 2.1 mmol/L, 2.1–2.6 mmol/L or > 2.6 mmol/L, serum P was < 1.1 mmol/L, 1.1–1.8 mmol/L or > 1.8 mmol/L, serum iPTH was < 150 ng/L, 150–300 ng/L or > 300 ng/L and Ca × P product was ≤ 4.4 mmol^2/L^2 or > 4.4 mmol^2/L^2 at the initial and final visits are presented in Table I. Table II shows the median values of anaemia parameters (serum Hb, ferritin concentrations and TSAT) and the percentage of patients whose serum Hb was < 110 g/L, 110–120 g/L and > 120 g/L, serum ferritin was < 224.7 pmol/L, 224.7–1797.6 pmol/L and > 1797.6 pmol/L, and TSAT was $< 20\%$, 20%–50% and $> 50\%$. The median values of lipid profiles with the percentage of patients in optimal values (total cholesterol ≤ 4.1 mmol/L, LDL cholesterol ≤ 2.6 mmol/L, HDL cholesterol > 0.9 mmol/L [males] and 1.2 mmol/L [females] and TG ≤ 2.3 mmol/L) as well as those whose values were out of these ranges are presented in Table III. Although 86 patients completed the study, some patients' data were unavailable for analysis, as the volume of blood submitted to the clinical laboratory was found to be insufficient.

As seen in Table I, the median Ca concentration increased in hypocalcaemic patients but decreased in hypercalcaemic patients, and the value was optimal in both groups by the end of the study period. In patients with hyperphosphataemia, there was a decline in median serum P levels, although it did not reach the target range. A downward trend in Ca × P product was observed in patients with Ca × P > 4.4 mmol^2/L^2. Improvement was also observed in the iPTH concentrations of patients whose baseline levels were suboptimal or supraoptimal, although the new levels did not fall within the target iPTH ranges. As presented in Table II, the median Hb concentration in anaemic patients increased, but not to target values. Unfortunately, the Hb concentration decreased in patients who were in the optimal or supraoptimal range at the beginning of the study. Serum ferritin reached the target values in all three groups of patients.

Total cholesterol levels improved to near-target values and LDL cholesterol levels decreased to optimal values in hypercholesterolaemic patients (Table III). Serum TG concentrations also decreased in patients with hypertriglyceridaemia, although the target values were not achieved. HDL cholesterol values were found to have decreased in most patients at the end of the study. Table IV shows the medications of the patients at the initiation of the study.

DISCUSSION

In most studies involving HD patients, phosphorus control is more challenging than other ESRD complications,[6,7] and even in a multidisciplinary clinic, achieving phosphorus control that meets the K/DOQI targets is very difficult.[6,8] 53% of patients in Thanamayooran et al's study[6] and 75% of subjects in Goldstein et al's study[9] had hyperphosphataemia at the start of dialysis. In the dialysis outcomes and practice patterns study, only 40% and 55% of patients achieved serum P levels and Ca × P product, respectively, that were within the target

Table I. Bone metabolism parameters in the subgroups* (n = 86).

Parameter	Below optimal range			Optimal range			Above optimal range		
	1st visit	Last visit	p-value	1st visit	Last visit	p-value	1st visit	Last visit	p-value
Ca (mmol/L)									
No. (%)	22 (26.5)	3 (3.6)	-	53(63.9)	67 (80.7)	0.034	8 (9.6)	13 (15.7)	-
Median; range	1.9; 1.7–2.1	2.4; 2.2–2.6	< 0.001	2.3; 2.1–2.5	2.4; 1.8–2.9	0.004	2.6; 2.6–2.9	2.4; 2.1–2.9	0.069
P (mmol/L)									
No. (%)	4 (4.8)	2 (2.4)	-	39 (46.4)	27 (32.1)	0.036	41 (48.8)	55 (65.5)	-
Median; range	0.97; 0.3–1.1	1.4; 1.1–1.6	-	1.6; 1.2–1.8	1.8; 1–2.9	< 0.001	2.3; 1.8– 3.3	2.1; 1.5–3.2	0.171
Ca x P ($mmol^2/L^2$)									
No. (%)	**	**	-	53 (63.1)	31 (36.9)	< 0.001	31 (36.9)	53 (63.1)	-
Median; range	**	**	**	3.4; 0.8–4.4	4.5; 2.5–7.1	< 0.001	5.5; 4.5–8.1	5.1; 4.1–8.1	0.224
iPTH (ng/L)									
No. (%)	18 (22.5)	15 (18.8)	-	18 (22.5)	22 (27.5)	1.000	44 (55)	43 (53.8)	-
Median; range	107.5; 28.0–149.7	125; 14.2–1,186.0	0.102	203.5; 151.3–284.0	222.0; 49.1–60.3	0.528	735.5; 307.0–4,678.0	532.0; 189.0–3,047.0	< 0.001

*Subgroups defined by K/DOQI 2003 guidelines and patients' parameter levels at initial visit. **Missing data. Smaller sample size in categories of each subgroup was included in Wilcoxon Signed Rank test.
Ca: calcium; P: phosphorous; iPTH: intact parathyroid hormone

Table II. Anaemia parameters in the subgroups.*

Parameter	Below optimal range			Optimal range			Above optimal range		
	1st visit	Last visit	p-value	1st visit	Last visit	p-value	1st visit	Last visit	p-value
Hb (g/L)									
No. (%)	60.0 (69.8)	69.0 (80.2)	-	16.0 (18.6)	13.0 (15.1)	0.664	10.0 (11.6)	4.0 (4.7)	-
Median; range	89; 56–109	91; 44–136	0.004	114; 110–119	105; 81–125	0.141	131; 122–155	103; 95–120	0.343
Serum ferritin (pmol/L)									
No. (%)	5.0 (6.2)	1.0 (1.2)	-	39.0 (48.8)	61.0 (76.2)	-	36.0 (45.0)	18.0 (22.5)	-
Median; range	96.2; 71.9–177.5	366.3; 139.3–1,141.5	**	1,006.9; 224.7–1,754.9	919.0; 280.9–3,523.3	0.183	2,970.5; 1,945.9–6,507.3	1,683.0; 712.3–3,145.8	< 0.001
TSAT (%)									
No. (%)	36.0 (46.7)	44.0 (58.7)	-	34.0 (45.3)	16.0 (34.7)	-	6.0 (0.08)	5.0 (6.7)	-
Median; range	13.1; 4.0–19.6	18.3; 4.8–61.0	0.003	28.7; 20.0–49.7	17.2; 4.8–58.6	< 0.001	60.0; 53.6–86.8	20.9; 7.3–67.0	**

*Subgroups defined by K/DOQI 2003 guidelines and patients' parameter levels at initial visit. **Missing data.
Hb: haemoglobin; TSAT: transferrin saturation

Table III. Lipid profile parameters in subgroups.*

Parameter	Below optimal range			Optimal range			Above optimal range		
	1st visit	Last visit	p-value	1st visit	Last visit	p-value	1st visit	Last visit	p-value
T-C (mmol/L)									
No. (%)	**	**	**	48.0 (58.5)	58.0 (70.7)	0.023	34.0 (41.5)	24.0 (29.3)	0.023
Median; range	**	**	**	3.2; 1.8–4.1	3.1; 1.7–4.5	0.861	4.8; 4.2–7.4	4.2; 2.5–5.6	< 0.001
LDL-C (mmol/L)									
No. (%)	**	**	-	58.0 (71.6)	64.0 (79.0)	0.115	23.0 (28.4)	17.0 (21.0)	-
Median; range	**	**	-	1.6; 0.3–2.6	1.8; 0.6–3.3	0.004	3.1; 2.6–4.9	2.4; 0.8–3.9	0.001
HDL-C (mmol/L)									
No. (%)	5.0 (6.2)	44.0 (54.4)	-	76.0 (93.8)	37.0 (45.6)	0.001	**	**	**
Median; range	1.0 ; 0.8–1.0	0.8; 0.6–1.7	0.127	1.3; 1.1–2.4	0.9; 0.4–1.2	< 0.001	**	**	**
TG (mmol/L)									
No. (%)	**	**	**	70.0 (86.4)	66.0 (81.5)	0.774	11.0 (13.6)	15.0 (18.5)	-
Median; range	**	**	**	1.2; 0.5–2.2	1.3; 0.4–3.8	0.165	2.8; 2.3–6.2	2.4; 1.3–5.6	0.033

*Subgroups defined by K/DOQI 2003 guidelines and patients' parameter levels at initial visit. **Missing data.
T-C: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; TG: triglycerides

values.[8] As seen in Table V, at the beginning of the study, serum Ca, P and iPTH concentrations, Ca × P product, serum Hb and ferritin levels in our patients were consistent with the findings of other researchers in our country.[4] Based on the report of Mahdavi-Mazdeh et al, only 1.8% of HD patients achieved all four target laboratory tests (bone metabolism, iPTH, Hb, ferritin), while 34.2% of patients achieved three targets and 75% achieved two targets.[4] In our study, although the median values of bone metabolism parameters improved over the study period in all the subgroups of patients, many patients remained outside the optimal target values, viz. hyperphosphataemia (65%), high Ca × P product (63%) as well as suboptimal and supraoptimal iPTH levels (18.8% and 53.8%, respectively). The use of calcium carbonate as the main phosphate binder and calcitriol as the main active vitamin D medication to control secondary hyperparathyroidism were the most important reasons for failure to meet NKF-K/DOQI targets for serum Ca, P and iPTH concentrations in our patients. A rapid increase in serum calcium and phosphate concentrations was observed following the administration of calcium carbonate and calcitriol, which led to a reduction in iPTH levels.

In a Canadian study aimed at assessing the outcomes of care in a nephrologist-supervised multidisciplinary clinic, CKD patients were monitored for up to four years. 26% of the ESRD patients were hypocalcaemic (mean Ca 2.2 mmol/L) at the initial visit, compared to 18% (mean Ca 2.3 mmol/L) at follow-up. Hyperphosphataemia was present despite the use of phosphate binder agents (almost exclusively calcium carbonate) in 43% of

Table IV. Types of medications.

Medication	No. (%)
Blood pressure medications	
β-blocker	30 (34.9)
ACEI/ARB	67 (77.9)
CCB	20 (23.3)
Diuretic	4 (4.7)
Others	20 (23.2)
Anaemia medications	
Erythropoietin	74 (86.0)
Iron sucrose	64 (74.4)
Bone metabolism medications	
Aluminium hydroxide	19 (22.1)
Calcium carbonate	69 (80.2)
Calcitriol	63 (73.3)
Sevelamer	31 (36.0)
Lipid profile medications	
Statin	25 (29.1)
Fibrates	0 (0.0)
Hyperglycaemia medications	
Insulin	12 (14.0)
Glibenclamide	2 (2.3)
Anti-platelet agents	
Aspirin	19 (22.1)
Dipyridamole/Plavix	4 (4.7)
Others	
Allopurinol	40 (46.5)
Pentoxifylline	3 (3.5)
Gabapentin	4 (4.7)

ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; CCB: calcium channel blocker

Table V. Patient distribution (%) in suboptimal, optimal and above optimal target ranges of bone metabolism and anaemia parameters in different studies.

ESRD complication	Present study		Mahdavi-Mazdeh[4]		Thanamayooran*[6]		Arenas[10]		Rivera[12]		Bannister[13]	
	1st visit	Last visit	1st visit	Last visit	1st visit	Last visit	1st visit	Last visit	1st visit	Last visit	1st visit	Last visit
Bone metabolism parameter												
Ca < 2.1 mmol/L	26.5	3.6	33.2	-	26.0	18.0	6.2	7.4	-	9.1	-	-
2.1 ≤ Ca ≤ 2.6 mmol/L	63.9	80.7	53.2	-	-	-	38.7	46.6	-	53.7	63.5	64.8
Ca > 2.6 mmol/L	9.6	15.7	13.6	-	-	-	55.0	44.4	-	37.1	-	-
P < 1.1 mmol/L	4.8	2.4	6.8	-	-	-	15.2	15.2	-	11.7	-	-
1.1 ≤ P ≤ 1.8 mmol/L	46.4	32.1	52.2	-	-	-	56.9	56.2	-	57.1	56	65
P > 1.8 mmol/L	48.8	65.5	41	-	53.0	43.0	27.8	28.8	-	31.1	-	-
Ca × P ≤ 4.4 $mmol^2/L^2$	63.1	36.9	75.1	-	-	-	-	-	-	95.1	88	91
Ca × P > 4.4 $mmol^2/L^2$	36.9	63.1	24.9	-	23.0	15.0	-	-	-	23.4	-	-
iPTH < 150 ng/L	22.5	18.8	27.7	-	-	-	53.8	31.4	-	25.1	-	-
150 ≤ iPTH ≤ 300 ng/L	22.5	27.5	24.2	-	-	-	25.6	18.7	-	31.2	10	10
iPTH > 300 ng/L	55.0	53.8	48.1	-	-	-	20.5	45.0	-	43.7	-	-
Anaemia parameters												
Hb < 110 g/L	69.8	80.2	-	-	51.0	31.0	-	-	-	-	-	-
110 ≤ Hb ≤ 120 g/L	18.6	15.1	-	-	-	-	-	-	-	-	65	66
Hb >120 g/L	11.6	4.7	-	-	-	-	-	-	-	-	-	-
Ferritin < 224.7 pmol/L	6.2	1.2	10.2	-	-	-	-	-	-	-	-	-
224.7 ≤ Ferritin ≤ 1,797.6 pmol/L	48.8	6.2	63.7	-	-	-	-	-	-	-	44	51
Ferritin > 1,797.6 pmol/L	45.0	22.5	26.1	-	-	-	-	-	-	-	-	-
TSAT < 20%	46.7	58.7	-	-	-	-	-	-	-	-	63	65
20% ≤ TSAT ≤ 50%	45.3	34.7	-	-	-	-	-	-	-	-	-	-
TSAT > 50%	6.7	8.0	-	-	-	-	-	-	-	-	-	-

*In this study, serum Hb < 10 g/dL and serum Ca < 8.4 mg/dL were considered the lower limits of the target range. Blank spaces (--) indicate missing data.
Ca: calcium; P: phosphorus; iPTH: intact parathyroid hormone; Hb; haemoglobin; TSAT: transferrin saturation

the ESRD patients with a mean serum P of 1.54 mmol/L at follow-up compared to 53% of patients at the initial visit with a mean P level of 1.8 mmol/L. 15% of patients at the four-year follow-up and 23% of patients at the initial visit showed Ca × P product of > 4.4 $mmol^2/L^2$. The clinic protocol delayed the use of erythropoietin in order to correct the iron stores with iron supplements. Nevertheless, the incidence of anaemia among ESRD patients increased over the course of the study, with 51% of patients found to be anaemic (mean Hb 100 g/L) at the initial visit compared to only 31% (mean Hb 107 g/L) at follow-up.[6] As summarised in Tables I and V, clinical pharmacists can play a more beneficial role in controlling bone disease in HD patients compared to the multidisciplinary clinics in developed countries.

The percentages of patients who were under, within and above the target values of serum iPTH concentration in our patients were comparable with the findings of Arenas et al;[10] however, normocalcaemia was achieved more frequently in our patients. In a multicentre study in Egypt, where all patients received calcium-based salts as phosphate binders, hyperphosphataemia and high Ca × P product were present in 69.1% and 30.2% of patients, respectively.[11] Hyperphosphataemia is a major concern in HD patients in developing countries. Dietary habits, ethnic factors, quality of dialysis, type of dialysis membrane and the economic factors that limit access to more expensive phosphate binders are some reasons for this concern.[11] Our study showed that the prevalence of hyperphosphataemia and high Ca × P product in Iranian patients is comparable to the findings in Egypt, with limitations that were similar to those that we encountered in the management of our patients.

Despite our limited access to new drugs compared to physicians in developed countries, the contributions of the clinical pharmacists at our centre played a major role in narrowing the differences in the results of attaining the K/DOQI target. Pharmacists also play a role in managing[12,13] adverse drug reactions and drug interactions as well as in providing dose titration in CKD and ESRD patients.[14] The major limitations of this study were our limited access to some preliminary drugs, the short duration of the study compared to other studies[6,13] and the single-centre activity of the clinical pharmacists, thus limiting the number of patients.

Although not ideal, the rates of attaining NKF-K/DOQI treatment targets in our patients were comparable to those in other countries. The participation of clinical pharmacists at the HD centre improved the control of CKD complications, including bone metabolism, anaemia and dyslipidaemia, compared to the previously adopted system of physician-only management of complications. Our study was limited by a fairly short study duration, data collection from a single HD centre and the limited use of newer treatment agents.

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