Potential effect of pharmaceutical care to improve outcomes in patients with chronic kidney disease-mineral bone disorder in Sulaimani dialysis centers

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Abstract:

Objective: the present study was aimed to evaluate the role of pharmaceutical services in improving the outcome of mineral bone disorder in patients with advanced chronic kidney disease.

Methodology: One hundred and twenty patients with chronic kidney disease-mineral bone disorder (CKD-MBD) screened for eligibility, seventy-six patients enrolled in the study and randomly allocated into two groups: pharmaceutical care and usual care, both groups interviewed by the pharmacist using specific questionnaire for assessing the quality of life (QoL). All the drug related problems (DRPs) including drug-drug interactions (DDIs) were recorded by the pharmacist. Blood samples were collected and utilized for analyzing the levels of vitamin D, phosphorous, calcium, albumin and parathyroid hormone at baseline and three months after. The pharmaceutical care group received all the educations about their medications and how to minimize DRPs; improve the QoL. Additionally, the pharmaceutical intervention included correcting the biochemical parameters.

Results: Pharmaceutical care significantly improved patients QoL and minimized DRPs and DDIs. It was also effective in improving the biochemical parameters.

Conclusion: Pharmaceutical care has a positive impact on improving the outcome of patients with CKD-MBD through attenuating DRPs, improving the biochemical parameters and the QoL.

Key words: CKD-MBD, Pharmaceutical care, biochemical parameters, QoL, DRPs.

الدور المحتمل للرعاية الصيدلانية في تحسين الوضع الصحى لمرضى الكلى المزمن المرافق لمرض العظام الايضي في مركز الديلزة في مدينة السليمانية

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الخلاصة:

لقد صممت هذه الدراسة لتقييم دور الرعاية الصيدلانية في تحسين الوضع الصحي لمرضى الكلى المزمن المرافق لمرض العظام الايضي. تمت معاينة مائة وعشرون مريض لغرض ادخالهم في الدراسة ولكن شروط الادخال توفرت في ستة و سبعين مريض فقط الذين تم توزيعهم الى فئتين, الفئة الاولى استلمت الرعاية الصيدلانية بينما الفئة الثانية استلمت الرعاية الاعتيادية المتبعة. تم مقابلة الفئتين من قبل الصيدلي الباحث باجراء استطلاع حول نمط وجودة الحياة والمشاكل

والتداخلات الدوائية مع اخذ عينة من الدم لفحص مستويات كل من فيتامين د3 و الكالسيوم و الفسفو واللالبومين وهورمون الغدة الدرقية. اثبتت النتائج ان الرعاية الصيدلانية ساهمت بشكل ملحوظ احصائيا بتحسين جودة الحياة وتقليل المشاكل والتداخلات الدوائية مقارنة بالفئة التي خضعت للرعاية الصحية الاعتيادية , علاوة على ذلك الرعاية الصيدلانية اسهمت ايضا في تحسين مستويات المؤشرات المختبرية للمرض.

الكلمات المفتاحية: مرض الكلى المزمن المرافق لمرض العظام الايضي, الرعاية الصيدلانية, المؤشرات المختبرية, جودة الحياة, المشاكل الدوائية.

Introduction

Disorders of mineral and bone metabolism are common in the CKD population characterized by abnormal level of vitamin D, parathyroid (PTH), calcium, phosphorus, fibroblast growth factor-23, bone turnover, as well as calcifications of soft-tissue. The disease may lead to changes in blood biochemistry, and bring about vascular calcification, which is a cause of significant morbidity [1].These alterations appear at stage 4 –5 CKD, however the disease starts much earlier [2]. It was formerly known as renal rickets then renal osteodystrophy, but later on the term CKD-mineral bone disorder (CKD-MBD) has been adopted [3].

The pathophysiology of this disorder is multifaceted, as kidney function drops; there is a decline in phosphate excretion, which results in hyperphosphatemia. Additionally, CKD progression causes decreased active vitamin D level and results in hypocalcemia and secondary hyperparathyroidism enhancing bone osteoclast activity. CKD-MBD mainly appears after some years of dialysis treatment [4, 5]. The changes that occur on the structure of the bone either due to high bone turnover state or a low bone turnover state [6]. CKD-MBD significantly increases mortality in CKD patients mainly through hyperphosphatemia that increase the risk of cardiovascular disease [7].

The primary goal of the treatment of CKD-MBD is reducing the level of phosphorous initially through the restriction of dietary phosphorus intake when the levels of phosphate or parathyroid hormone start to increase [8]. Beside phosphate binders, vitamin D may be needed to elevate calcium level adequately to suppress parathyroid hormone secretion. Patients can also be given calcimimetics [6].

Recently, pharmaceutical care began to have pronounced role in improving the outcome of CKD. The orientation of pharmaceutical care has been developed from the drug to the patient-drug therapy and how it should be optimized for the individual patient [9]. Multiple comorbidities and polypharmacy render patients with CKD at risk for drug-related problems (DRPs) [10, 11]. Clinical pharmacy services can have a pivotal role in improving patient care, although only few studies highlighted the impact of clinical pharmacy services in CKD, most of them share the positive role of pharmacist in identification and prevention of DRPs [12, 13], improving quality of life [14], improving economic outcomes [15] , and decreasing the progression and frequency of hospitalization [16]. The underutilization of clinical pharmacists contributes in increasing the incidence of DRPs [17]. In some developing countries like Iraq patient-oriented pharmaceutical care is still not implemented properly, accordingly the present study was designed to evaluate the role of pharmaceutical services in improving the outcome of mineral bone disease in patients with advanced chronic kidney diseases through identification and management of DRPs including drug-drug interactions, improving the QoL, and increasing patients adherence.

Methodology

The study protocol was approved by the Ethical Committee of the Faculty of Medical Sciences/University of Sulaimani, and carried out in accordance with the principles of the Declaration of Helsinki as revised in 2000 (18); all patients gave informed consent.

Patients Selection and Randomization

The study was conducted between March 2019 to September 2019 at two dialysis centers in Sulaimani city (Qirga and Shar teaching hospital dialysis center). Pre dialysis patients were recruited from private clinics according to the selection criteria. Patients on maintenance hemodialysis were contacted on the days of their dialysis and, when confirmed eligible for enrolment, were given study information before recruitment. The pre dialysis patients were contacted on their clinic days. One hundred and twenty patients were screened for eligibility, and only 76 patients met the inclusion criteria and enrolled in the study (Figure 1).

The inclusion criteria included patients of both sexes with age ranging from 18 to 65 years and they were either with advanced CKD stage (4 or 5) or on hemodialysis. After taking the demographic data, the patients were randomized into two groups, 38 patients were allocated to each of the pharmaceutical care group and usual care group. The first group received pharmaceutical care from a pharmacist who performed an interview with each patient and his/her caregiver to evaluate the patient's medication adherence and to identify any DRPs including drug selection, drug form, dose selection, treatment duration, dispensing, drug use/process, patient related and others.

The patients were evaluated for serum albumin as well as bone metabolism parameters (vitamin D, corrected total serum calcium, serum phosphorus, and PTH concentrations) at the beginning of the study and three months after, eGFR was also calculated at the baseline. During the three months, the pharmacist interviewed each patient and/or caregiver every two week and reviewed related medications, including phosphate binders (calcium carbonate, and sevelamer), alfacalcidol, and the DRPs were detected and recommendations were proposed to the prescribers to adjust the dosage of these drugs according to the laboratory investigation results and to resolve the DRPs.

For patients with vitamin D deficiency or insufficiency, the pharmacist suggested to the prescriber to add vitamin D_3 according to the Kidney Disease Outcomes Quality Initiative (KDOQI) clinical practice guidelines for bone metabolism and disease in chronic kidney disease (8). Patients were also counseled and received all the necessary information and educations about their disease, medications (correct administration, their adverse effects, drug-drug interactions (DDIs)), and lifestyle modification. The second group was on usual care without pharmaceutical care. The same laboratory tests were done for both groups at the beginning of the study and three months after.

Data collection

A structured questionnaire was used to collect patients' demographic characteristics, co-morbid disease, and medications history. Medscape interaction database [19] was used to check for drug interactions, according to this database drug interactions are classified into five categories; none, minor, significant (monitor closely), serious (use alternative), contraindicated. The 12-Item Short-Form health survey (SF-12) was used to assess quality of life [20]. DRPs were classified using the Pharmaceutical Care Network Europe Foundation classification system (PCNE V8.02) [21], according to this tool, there are eight main types of DRPs including drug selection, drug form, dose selection, treatment duration, dispensing, drug use process, patient related, and others. Blood sample was collected from each patient at zero time and 90 days after for measuring parathyroid hormone, vitamin D, total calcium, phosphorous and albumin levels.

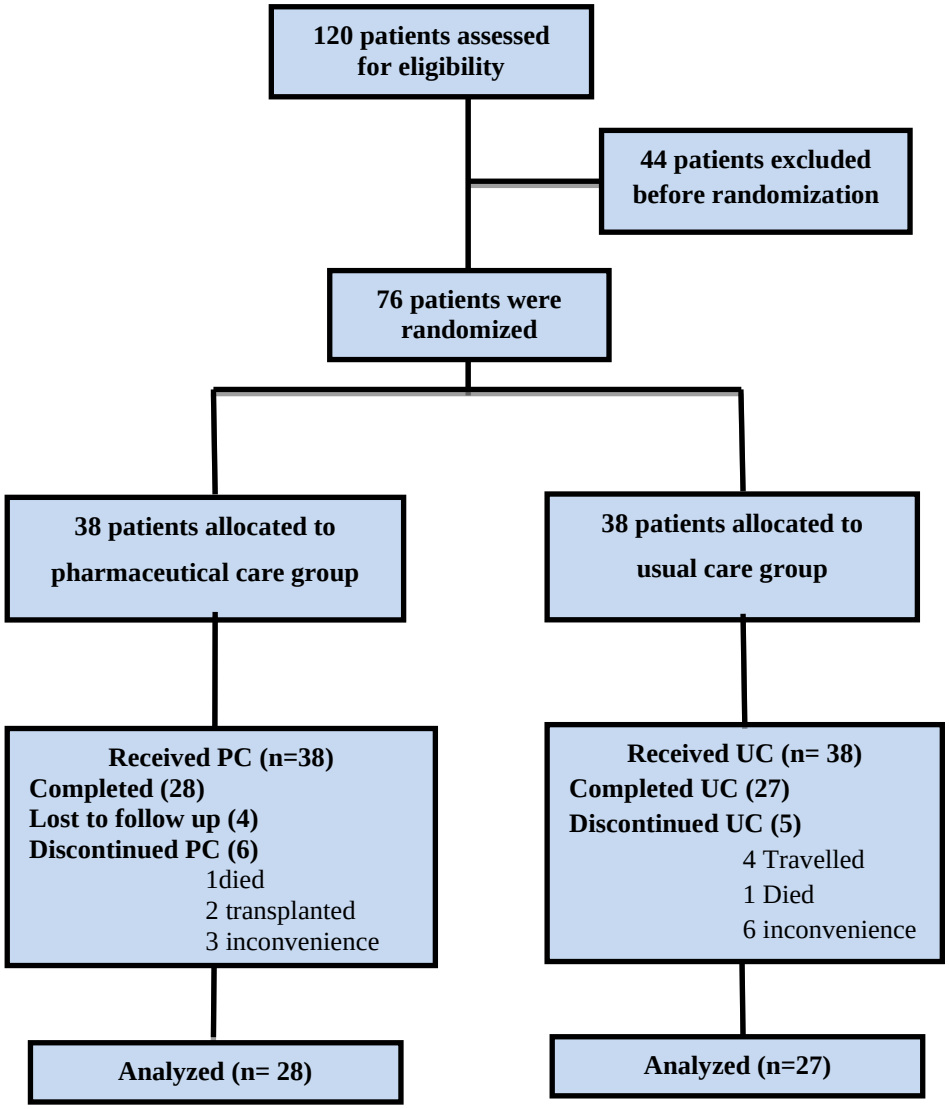

Figure (1): Flowchart displaying the participant's screening, randomization, and intervention.

Statistical Analysis

Data were analyzed using the statistical package for social sciences version 17 (released 2008; SPSS Inc., Chicago, IL, USA). Results were presented in tabular form. Discrete variables were presented as frequency and percentages. Continuous variables were presented as mean ± standard deviation. The chi-square test was used to determine the significance of association between discrete variables. Paired t-test was used to determine the difference between pre and post usual care or pharmaceutical care values. Unpaired t-test was utilized to evaluate the differences between post usual care and post pharmaceutical care. P –value ≤ 0.05 was considered statistically significant.

Results

Baseline characteristics

Baseline demographic data of the studied sample (Table 1) showed no significant differences between both groups regarding the age, gender, BMI, employment, educational status, comorbidity and the stage of CKD.

Table (1): Baseline characteristics of the study sample

	Usual care (n =27)	Pharmaceutical care (n =28)	
Characteristics	n (%) /mean ± SD	n (%) /mean ± SD	P-value
Age (years)			
18-25	2 (7.4)	2 (7.1)	0.99
26-35	0 (0.0)	1 (3.6)	0.99
36-45	6 (22.2)	5 (17.9)	0.746
46-55	6 (22.2)	7 (25)	0.8
56-65	13 (48.1)	13 (46.4)	0.898
Height (cm)	169 ± 6.7	170 ±9.5	0.60
Weight (kg)	69.4 ± 15.8	71.1 ±15.7	0.68
BMI (kg/m^2)	24.39 ± 5.36	24.5 ± 3.9	0.92
BMI Range			
Underweight	3 (11.1)	1 (3.6)	0.352
Normal weight	14 (51.9)	17 (60.7)	0.5
Overweight	5 (18.5)	8 (28.6)	0.38
Obese	5 (18.5)	2 (7.1)	0.252
Gender			
Male	13 (48.1)	15 (53.6)	0.688
Female	14 (51.9)	13 (46.4)	0.69
Marital status			
Single	7 (25.9)	4 (14.3)	0.281
Married	20 (74.1)	24 (85.7)	0.28
Employment			
Student	1 (3.7)	0 (0.0)	0.99
Employed	4 (14.8)	3 (10.7)	0.7
Self-employed	0 (0.0)	4 (14.3)	0.11
Retired	4 (14.8)	1 (3.6)	0.193
Unable to work	9 (33.3)	7 (25)	0.496
Home-maker	9 (33.3)	13 (46.4)	0.322
Education			
Less than high school	17 (63)	23 (82.14)	0.11
High school	9 (33.3)	4 (14.28)	0.096
Technical degree or diploma	1 (3.7)	0 (0.0)	0.99
College degree or diploma	0 (0.0)	1 (3.6)	0.99
Comorbidities			
Diabetes	8 (29.6)	11 (39.3)	0.45
Hypertension	22 (81.5)	26 (92.9)	0.25
Dyslipidemia	6 (22.2)	8 (28.6)	0.59
Coronary artery disease	6 (22.2)	6 (21.4)	0.94
Heart failure	2 (7.4)	0 (0.0)	0.24
Other	3 (11.1)	7 (25)	0.18
CKD stage			
Stage 4	5 (18.5)	3 (10.7)	0.412
Stage 5	0 (0.0)	2 (7.1)	0.491
Dialysis	22 (81.5)	23 (82.1)	0.949
Mean GFR (ml/min) in stage 4 patients	25.1 (4.3)	25.9 (0.18)	0.16
Mean GFR (ml/min) in dialysis patients	8.314 (2.98)	8.88 (3.1)	0.53
Mean number of medications	7.15 ± 3.5	7.89 ± 2.4	0.36
Number of medications			
1-5	9 (33.3)	5 (17.9)	0.188
6-10	14 (51.9)	17 (60.7)	0.508
11-15	2 (7.4)	5 (17.9)	0.422
>16	2 (7.4)	1 (3.6)	0.611

Data are presented as percent or mean ± SD: n: number of patients, %: percentage of patients. Chi-square and unpaired t-test were utilized to predict significance at $P<0.05$.

Effect of pharmaceutical care on patient's quality of life

The mental component summary (MCS) of the quality of life has been improved significantly in the group with pharmaceutical care (P-value= 0.034) and non-significant improvement of the physical component summary (PCS) (P-value= 0.681), while the group with the usual care showed a non-significant increase in both PCS and MCS (P-value= 0.834 and P-value= 0.162) respectively. No significant changes were seen in both MCS and PCS when the comparison done between both groups at the end of the study (Table 2).

Table (2): Effect of pharmaceutical care on patient's quality of life

Quality of life (SF12)	Usual care n = 27			Pharmaceutical care n = 28			
	Baseline mean ± SD	After 3 months mean ± SD	P-value	Baseline mean ± SD	After 3 months mean ± SD	P-value	*P-value
PCS-12	32.49 ± 8.14	32.59 ± 8.15	0.834	35.25 ± 7.59	35.80 ± 6.826	0.681	0.119
MCS-12	42.10 ±10.828	44.01 ± 11.44	0.162	43.22 ±13.18	46.97 ± 8.21	0.034	0.273

Data are presented as mean ± SD, n: number of patients
P-value: comparison within the same group at the end of the study (paired t-test)
*P-value: comparison between UC and PC groups at the end of the study (unpaired t-test)

Effect of pharmaceutical care on DRPs

Pharmaceutical care revealed a significant attenuation in DRPs compared to baseline value (P-value= 0.001). Whereas patients with usual care revealed a significant increase in DRPs compared to baseline value (P-value= 0.022). Moreover, a significant difference was observed between both groups' ant the end of the study (P-value= 0.0001), (Table 3).

Table (3): Effect of pharmaceutical care on DRPs

DRPs	Usual Care n = 27			Pharmaceutical Care n = 28			
	Baseline mean ± SD	After 3 months mean ± SD	P-value	Baseline mean ± SD	After 3 months mean ± SD	P-value	*P-value
	1.815 ± 1.21	2.37 ± 1.305	0.022	2.607±1.547	0.857 ± 0.525	0.001	0.0001

Data are presented as mean ± SD, n: number of patients
P-value: comparison within the same group at the end of the study (paired t-test)
*P-value: comparison between UC and PC groups at the end of the study (unpaired t-test)

The most significant change in the types of DRPs were drug selection and dispensing (P-value < 0.0001) when compared with baseline value and with the usual care group at the end of the study. Drug use/ process was also significantly decreased when compared to the baseline value (P-value<0.05). Additionally, a non-significant decrease in each of dose selection (P-value = 0.143), treatment duration (P-value = 0.236), and patient related (P-value = 0.11) were observed (Table 4).

Table (4): Effect of pharmaceutical care on the types of DRPs

Types of DRPs	Usual Care n=27			Pharmaceutical Care n=28			
	Baseline %	After 3 months %	P-value	Baseline %	After 3 months %	P-value	*P-value
Drug selection	59.26%	77.78%	0.143	75%	11%	0.0001	0.0001
Dose selection	7.41%	14.81%	0.669	(25%)	7.14%	0.143	0.317
Treatment duration	0%	7.41%	0.491	10.71%	0%	0.236	0.236
Dispensing	48.15%	51.85%	0.785	46%	0%	0.0001	0.0001
Drug use/process	3.70%	7.41%	0.99	21%	0%	0.023	0.236
Patient related	3.70%	7.41%	0.99	14.29%	0%	0.11	0.236
Other	59.26%	70.37%	0.393	67.86%	67.86%	0.99	0.84

Data are presented as percentage of patients with each type of DRP, n: number of patients
P-value: comparison within the same group at the end of the study (chi square test)
*P-value: comparison between UC and PC groups at the end of the study (chi square test)

Effect of pharmaceutical care on DDIs

In the current study pharmaceutical care group exhibited a significant decrease in the number of drug interactions when compared with the baseline value (P-value = 0.001) and with usual care group at the end of the study (P-value = 0.048), (Table 5). The types of interactions were ranging from minor to significant with P-value < 0.05 for both. The results also showed a significant decrease in the significant type of interactions when compared with usual care group at the end of the study (P-value = 0.015). While the usual care group showed a non-significant increase in the number of drug interactions (P-value > 0.05) for both types (Table 6). The most common minor interaction was between calcium and furosemide and the most common significant interaction was between calcium and amlodipine (Table 7).

Table (5): Effect of pharmaceutical care on Drug interactions

Drug interactions	Usual Care n =27			Pharmaceutical Care n =28			
	Baseline mean ± SD	After 3 months mean ± SD	P-value	Baseline mean ± SD	After 3 months mean ± SD	P-value	*P-value
	1.59 ± 0.844	1.81 ± 0.921	0.11	1.46 ±0.99	1 ± 0.816	0.001	0.048

Data are presented as mean ± SD, n: number of patients
P-value: comparison within the same group at the end of the study (paired t-test)
*P-value: comparison between UC and PC groups at the end of the study (unpaired t-test)

Table (6): Effect of pharmaceutical care on types of drug interactions

Type of drug interactions	Usual Care n=27			Pharmaceutical Care n=28			
	Baseline	After 3 months	P-value	Baseline	After 3 months	P-value	*P-value
Minor interaction	12	15	0.18	16	12	0.043	0.485
Significant interaction	31	34	0.33	25	16	0.026	0.015

Data are presented as number of interactions, n: number of patients
P-value: comparison within the same group at the end of the study (chi square test)
*P-value: comparison between UC and PC groups at the end of the study (chi square test)

Table (7): The most common minor and significant drug interactions

List of Minor interactions	**Frequency**
Calcium + Furosemide	32
Calcium + Aspirin	8
Calcium + Iron	6
Calcium + Bumetanide	4
Calcium + Sulfasalazine	2
Calcium+ Budesonide	2
Thiazide + calcium	1
List of Significant interactions	**Frequency**
Calcium + Amlodipine	40
Calcium + Metoprolol	22
Calcium + Bisoprolol	8
Calcium + Carvedilol	6
Calcium + Atenolol	4
Calcium + Labetalol	4
Calcium + Felodipine	4
Calcium + Allopurinol	4
Calcium + Gabapentin	3
Calcium + Ramipril	2
Calcium+ Diltiazem	2
Calcium + Ciprofloxacin	1
Calcium + Levothyroxine	1
Calcium + Nebivolol	1
Calcium + Rosuvastatin	1

Effect of pharmaceutical care on Biochemical parameters

Pharmaceutical care produced a significant increase in the level of Vitamin D when compared to the baseline value (P-value= 0.001) and with usual care group at the end of the study (P-value = 0.002).

Table (8): Effect of pharmaceutical care on bone metabolism parameters.

Parameter (unit)	Usual Care n= 27			Pharmaceutical Care n= 28			
	Baseline mean ± SD	After 3 months mean ± SD	P-value	Baseline mean ± SD	After 3 months mean ± SD	P-value	*P-value
Vitamin D (ng/ml)	20.75±16.64	20.403 ± 16.13	0.768	12.94±9.29	33.65± 13.53	0.001	0.002
PTH (pg/ml)	260.69±175.54	284.65 ± 212.68	0.36	284.55±212.67	178.7±135.5	0.001	0.034
Calcium (mg/dL)	8.58 ±1.163	8.628 ± 0.945	0.81	9.15 ±1.011	9.11 ± 0.758	0.78	0.041
PO_4 (mg/dL)	4.83 ±1.186	5.018 ±1.773	0.54	4.754±1.19	4.406 ± 1.044	0.079	0.123
Albumin (g/dL)	3.87 ± 0.519	3.75 ± 0.433	0.141	3.8± 0.446	3.93 ± 0.384	0.137	0.097

Data are presented as mean ±SD, n: number of patients
P-value: comparison within the same group at the end of the study (paired t-test)
*P-value: comparison between UC and PC groups at the end of the study (unpaired t-test)

Parathyroid hormone was significantly decreased when compared to the baseline value (P-value= 0.001) and with usual care group at the end of the study (P-value = 0.034), furthermore, a non-significant decrease in the level of phosphorous (P-value=0.079) was observed when compared to the baseline value and with usual care group at the end of the study (P-value = 0.123). No significant change was seen in calcium and albumin levels when compared to the baseline value (P-value= 0.78), (P-value= 0.137) respectively, but there was a significant increase in calcium level when compared with the usual care group at the end of the study (P-value = 0.041). Patients received the usual care showed no change in the above parameters (Table 8).

Discussion

Patients with chronic kidney disease (CKD) experience high rates of hospitalization and readmission, mortality and reduced life expectancy [22-24]. Most patients have co-morbid conditions such as cardiovascular and mineral bone diseases [25]

To our knowledge, this will be the first study introducing pharmaceutical care to patients with CKD-MBD in Sulaimani.

Based on the findings of this study, pharmaceutical care was effective in improving outcomes of patients with CKD-MBD through improving the QoL, decreasing DRPs and DDIs.

The quality of life was assessed using the SF-12. Pharmaceutical care showed significant and non-significant improvement in MCS and PCS respectively. Pharmaceutical care can significantly improve the QoL scores over time in the domains of physical and mental functioning [14, 25, 26].

Studies have proven that more than 50% of DRPs can be avoided via interventions suggested by clinical pharmacists to solve or prevent these problems [26, 27], and this finding was obvious in the present study that revealed a significant decrease in DRPs.

Regarding DDIs, the study showed that drug interactions was less than that reported by other studies [28], this could be attributed to the fact that we only included interactions involving medications used in management of MBD. Interaction between calcium carbonate and amlodipine was the most common interaction in our study, this

is in tune with the findings of Al-Ramahi et al (27).

The primary target for management of CKD-MBD is to normalize the biochemical parameters such as hyperphosphataemia, vitamin D deficiency and hyperparathyroidism and to prevent bone manifestations, cardiovascular and extravascular calcifications, and the associated morbidity and mortality with both nonpharmacologic and pharmacologic interventions.

The results indicate that vitamin D deficiency can be effectively corrected by administration of nutritional vitamin D to patients with advanced CKD. Similar findings are reported by previous studies [29, 30].

Phosphorous level has been decreased in PC group, although the reduction was not significant, but in comparison to the usual care group, it is obvious that pharmaceutical care has a positive impact and can help the patients to decrease hyperphosphatemia and achieve their treatment goals for phosphorus. According to previous studies performed in hemodialysis patients, it has been observed that phosphorus control is a difficult process, achieving K/DOQI targets was even challenging in a multidisciplinary clinic [31]. The non-significant change in PO_4 in the present study may be explained by several points including; the use of alfacalcidol as the only active vitamin D medication to control secondary hyperparathyroidism, furthermore, in this study cholecalciferol has been used to manage vitamin D deficiency in majority of the patients in PC group, these may contribute to the results being not significant. Additionally, the baseline PO_4 level was not that high and 60.71% of the patients were in target range for PO_4, so most of them did not require aggressive phosphate binding therapy. Similar to our findings, previous studies indicate that pharmaceutical care can improve the management of hyperphosphatemia [31, 32].

In a study conducted by Roberts-Clary et al.[32] aimed to the contribution of pharmaceutical care in CKD-MBD management, they found that patients are more likely to achieve their laboratory targets for PO_4, the improvements associated with pharmacy care after 3 months of enrollment, and were maintained throughout the year of follow up.

The mean corrected calcium remained almost the same at the end of the study in both groups, however, a higher percentage of patients in PC group were in optimal calcium range at the end of the study (82.1%) in comparison with the UC group (44.4%). Pharmaceutical care effectively helps CKD patients to achieve their calcium goals [31] Furthermore, no significant change seen in serum albumin level in either group, while a significant reduction in the mean serum parathyroid hormone level in PC group was observed. Other studies proved that the active participation of pharmacists as a member of the medical team in the management of patients undergoing hemodialysis who had secondary hyperparathyroidism, resulted in a significant reduction in the proportion of patients with moderate to severe hyperparathyroidism, in addition, the costs of care have been also decreased in comparison with usual treatment that did not include a pharmacist [33].

Conclusion

Based on the above findings, this study can conclude that pharmaceutical care has a positive impact on improving the outcome of patients with CKD-MBD through attenuating DRPs and improving the biochemical parameters and the QoL.

Limitations

The major limitations of this study are the small sample size, and relatively short duration. Therefore, future studies are warranted to determine the long-term effect of pharmaceutical care and on a larger study population.

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