Scholars Academic Journal of Pharmacy
Abbreviated Key Title: Sch Acad J Pharm
ISSN 2347-9531 (Print) | ISSN 2320-4206 (Online)
Journal homepage: http://saspublishers.com

OPEN ACCESS
Pharmacy

Role of Clinical Pharmacist in the Management of Anemia in Dialysis Patients

Mahdi Hani Al Farhan[1*]

[1]Clinical Pharmacist, the Royal Medical Services, Amman, Jordan

DOI: 10.36347/sajp.2021.v10i10.002 | **Received:** 09.09.2021 | **Accepted:** 15.10.2021 | **Published:** 30.10.2021

***Corresponding author:** Mahdi Hani Al Farhan

Abstract **Original Research Article**

Background: Anemia management is complicated in patients with End Stage Renal Disease (ESRD) on hemodialysis. Clinical pharmacists have been involved in the care of ESRD patients in various settings. ***Aims of the study:*** The aim of this study was to explore the therapeutic and pharmacoeconomic outcome of a clinical pharmacist- implemented anemia management in dialysis patients through a randomized, controlled, open label design clinical study. ***Methods:*** The study was carried out over a period of three months at renal /hemodialysis unit of King Hussein Medical Center at the Royal Medical Services**.** A total 203 patients of both genders on hemodialysis were randomized into an intervention or control arm, 102 patients were allocated to the intervention arm and 101 patients to the control arm. In the intervention arm, patients received physician-pharmacist collaborative care. In the control arm, patients received usual care. ***Results:*** In this study, clinical pharmacist interventions had a positive impact on achieving target goal of Hb concentrations among HD patients. The percent of patients who achieved target Hb and Hct at the end of the study was 87.2% in the intervention arm versus 36.6% in the control arm, $p = 0.02$). Patients in the intervention arm used less epoetin α, leading to a savings of 5723.4 JD. The average amount of epoetin α vials used in the intervention arm was significantly lower than that in the control arm ($p = 0.002$). ***Conclusion:*** Clinical pharmacists can positively contribute to the care of ESRD patients and reduce the gaps in current patient care.

Keywords: Anemia, Hemodialysis, Clinical pharmacist, Hemoglobin.

BACKGROUND

Chronic kidney disease (CKD) represents a major public health problem in developed and developing countries. It is estimated that about 10% of the adult U.S. population is suffering from CKD [1]. CKD defined as the presence of kidney damage or decreased kidney function for three or more months. The European Kidney Health Alliance (EKHA) reports that approximately 10% of European citizens are affected by some degree of CKD [2]. In Jordan; CKD has been growing rapidly in recent years and more than 746 people per million were receiving hemodialysis in 2012, an increase from the previous year of 1.1% [3]. CKD and end-stage renal disease (ESRD) are associated with an increased risk of mortality and morbidity, and reduced average life expectancy [4].

Chronic kidney disease (CKD) describes the continuum of kidney dysfunction from early to late-stage disease. Estimated glomerular filtration rates (eGFR) range from 90 L/minute/ 1.73 m² in the early stages to less than 15 mL/minute/1.73m² in the end stage of the disease. CKD is a major medical problem among communities, which needs early assessment to delay progression [5]. When disease progresses to a stage where kidney failure occurs, patients are required to start renal replacement therapies, either through dialysis or transplantation [6].

As CKD progress from early stages (stage 1, 2 and 3) to late stages (stage 4 and 5), this will lead in the appearance of new symptoms and concomitant complications [7]. Common complications and co-morbidities of CKD include fluid and electrolyte disturbances, anemia, bone and mineral disease, in addition to hypertension, dyslipidemia, metabolic acidosis, and many co-morbidities including malnutrition, pruritus and uremic bleeding [8]. CKD patients have an increased risk of developing cardiovascular disease (CVD), which may present as coronary heart disease (CHD), cerebrovascular disease, peripheral vascular disease, and heart failure.

The management of frequent and life-threatening co-morbidities (either as causes or complications of CKD) and the prevention or delay of its progression to ESRD is multifactorial. In stage 5 CKD patients, the decision to initiate of renal

replacement therapies (RRTs), such as hemodialysis (HD) or peritoneal dialysis (PD) is usually prescribed to relieve uremic toxins whereas kidney transplantation is the therapy of choice for ESRD [8].

Anemia is prevalent among patients with CKD and is an important risk factor for cardiovascular illness [9]. The anemia of CKD is usually described as a normocytic, normochromic form occurring in ESRD. In patients suffering from CKD or ESRD; there is a significant deficiency of erythropoietin production and an inadequate response to hypoxia, resulting in an inability to produce adequate mature red blood cells (RBCs). In addition to diminished production of erythropoietin, patients suffering from CKD may have other causes contributing to anemia. This includes a shortened life span of RBCs in the presence of uremia; deficiencies in iron, folic acid, and vitamin B_{12}, and blood loss during hemodialysis.

The possibility of developing anemia is several times greater in those with renal insufficiency compared to the general U.S population, and recent evidence showed that anemia occurs earlier in CKD than previously thought, particularly in diabetic nephropathy [10]. Observational studies showed that anemia in CKD is associated with elevated risk for cardiovascular disease, hospitalization for cardiac disease, death from congestive heart failure (CHF), and all-cause mortality.

Erythropoietin stimulating agents (ESAs) are commonly used to treat anemia, especially in patients with CKD. However, they are not without risks. Optimal treatment with ESAs, such as epoetin-alfa and darbepoetin-alfa, requires close monitoring of hemoglobin response, iron stores, co-morbidities, and concurrent medications [11].

Management of anemia of CKD with ESAs and various iron supplementations in Hemodialysis (HD) patients has many clinical challenges, including keeping stable hemoglobin levels within narrow therapeutic goal ranges, modifying iron and ESAs dosages, and improving the response to erythropoietin to reach the lowest possible effective erythropoietin dosage[12].

In recognition of this setting, clinical practice guidelines such as the “2012 KDIGO Clinical Practice Guideline for Anemia in CKD,” with recommended targets for hemoglobin (10—11.5 g/dl) and iron indices (transferrin saturations (TSat) < 30%, ferritin< 500 ng/ml), provide strategies, not a coherent set of rules. The aim of the recommendations is to aid in decision-making, not provide regulations for clinical management. Furthermore, successful and efficient tools of employing these strategies into clinical practice have yet to be more explored. The efficacious participation of pharmacists in ESAs and various iron replacement therapies for anemia in HD patients is recommended.

As medication experts, clinical pharmacists are well qualified to manage complicated drug therapies requiring thorough monitoring [13]. The complexity of management, risks associated with inappropriate treatment and high cost of ESA therapy make patients on these medications’ excellent candidates for pharmacist-based management.

AIMS AND OBJECTIVES

This study will assess the therapeutic and pharmacoeconomic outcomes of Clinical Pharmacist-Implemented Anemia Management in dialysis patients through a randomized controlled trial (RCT). The results of this study will serve to enforce the role of clinical pharmacy in optimizing treatment of anemia in dialysis patients.

Laboratory Evaluation

Laboratory data that will be assessed during the study**:**

a. Hemoglobin (Hb).

b. White blood cell (WBCs), and platelet count (Plt).

c. Mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC).

d. Red blood cell distribution width (RDW).

e. Iron parameters:

- Serum iron.
- Total Iron Binding Capacity (TIBC).
- Percent transferrin saturation (serum iron × 100 divided by TIBC) [TSAT].
- Serum ferritin.

f. Serum B12 and plasma folate levels.

METHODS

Study Design

A randomized, controlled, open label designed clinical trial was carried out over a period of 3 months, at which patients were followed up every two weeks.

The study began in April 2015 and ended by July 2015 with a sample of 203 patients who were receiving maintenance HD at the outpatient dialysis unit at King Hussein Medical Center (KHMC) at the Jordan Royal Medical Services (JRMS).

Ethical approval

The study was approved by the Scientific Committee of the Faculty of Pharmacy and the Faculty of Postgraduate Studies at the University of Jordan. In addition, ethical approval has also been obtained from the IRB committees at the JRMS.

STUDY SUBJECTS

The study subjects included all HD participants in the renal /hemodialysis unit of KHMC who met the inclusion criteria and the exclusion criteria.

Each arm (control and intervention) was classified into 3 age groups (20-40 years, 40-60 years and >60 years). Each group includes 2 phases, correction phase (in which Hb is below 10 g/dl or Hb above 12 g/dl) and maintenance phase (in which Hb is 10-12 g/dl).

Inclusion Criteria

- Patients on hemodialysis for more than 3 months and patients provided written informed consent to their participation in the research.

Exclusion criteria

- Patients < 18 years, pregnant patients, patients with dementia and cognitive impairment and patients with poly cystic kidney disease.

DATA COLLECTION FORM

All patients who agreed to participate in the study were interviewed by the clinical pharmacist in order to obtain details on social and medical history.

Identification of TRPs regarding renal anemia

Patients' medical problems regarding anemia were weighed against JRMS protocol for the management of anemia in CKD patients.

Classification of TRPs

For the classification of treatment –related issues we used (AbuRuz, *et al.*, 2006) [14] system.

Intervention group

Each patient was met by the researcher once a week and all patients were:

1. Educated about the definition, nature and symptoms of chronic kidney disease.
2. Educated about goals of anemia management and medications used for management of renal anemia.
3. Encouraged to adhere to both pharmacological and non-pharmacological treatments.
4. Educated about the symptoms of anemia in HD patients.

All patients were educated by the clinical pharmacist verbally and by providing the patient with educational material.

Communicating TRPs

Recommendations were submitted using pharmacist consult note. The consult note provided by the pharmacist described objective or subjective findings related to the recommendation, explained the TRP or patients' therapeutic needs. Subsequently, all recommendations were collected for the patients who needed intervention in the intervention group and discussed with responsible physician who in turn accepts or rejects the recommendation as part of the overall treatment plan.

Control group

Patients in the control arm did not receive any advice by the clinical pharmacist; however, they received their normal care by other member of medical team. All TRPs were identified. However, no consult notes or pharmaceutical care plans (PCP) were communicated to the physician and the patient received the normal care.

Follow up

Both study groups were followed-up for three months after enrollment in the study. Interventional arm was followed every week, 2 weeks and one-month intervals according to the lab tests requested and the intervention made by the clinical pharmacist, while the control arm were followed once a month. At the follow up, there was an assessment of the objective.

Outcome Measurements

The main outcomes measures of this study were

- The number of patients who achieved the target goal of Hb according to the JRMS protocol of anemia management.
- The number of patients who transferred from the correction phase to the maintenance phase.
- The consumption level of Epotein-α by the patients in the intervention group compared with the control group.

DATA ANALYSIS

Data analysis was conducted using SPSS version (22). Descriptive analyses were reported as were reported as Mean ± standard deviation (SD), and percentage. When comparing continuous variables within research groups in the same study arm, between baseline and end of the study, independent t-test was used. On the other hand, when comparing continuous variables between interventional and control groups of the same age category ANOVA (repeated measure) test was used, Chi square test was used for discrete variables, and Pearson test was used to find the correlation between depression and the value of Hb. The significance level was set at 0.05.

RESULTS

Description of Study Sample

A total of 203 patients of both genders agreed to be enrolled in the study, of which 102 patients were allocated to the intervention and 101 patients to the control groups. Each group was divided into 3 age groups (Figure 1). Both study groups received medical care by the same team of physicians. Medical care team included two nephrologists with consultant grade, two nephrologists with senior specialist grade and three fellow residents in nephrology specialty.

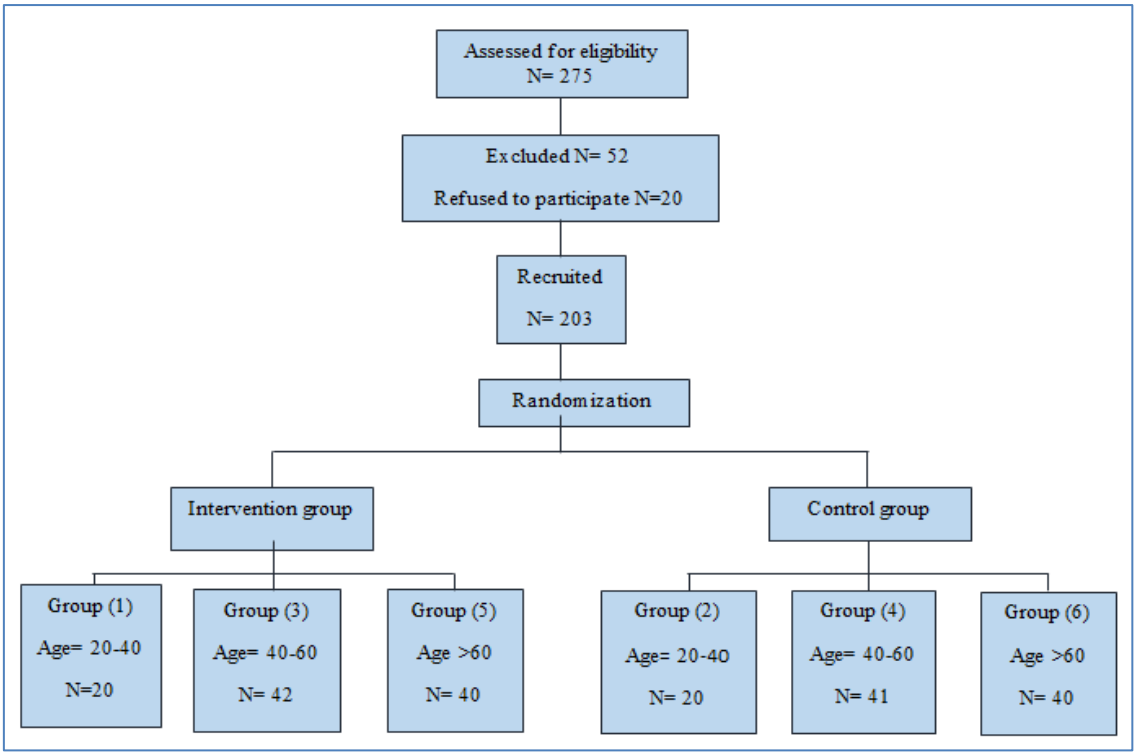

Fig-1: Flow chart of the study procedure: the role of clinical pharmacist in the management of anemia in hemodialysis patients

Patients Demographics

Table-1: Description of demographic characteristics of patients in the control and intervention groups (n=203)

Patient's study group	**Intervention group**			**Control group**		
Group No.	**Group 1. N (%)[1]**	**Group 3. N (%)[1]**	**Group 5. N (%)[1]**	**Group 2. N (%)[1]**	**Group 4. N (%)[1]**	**Group 6. N (%)[1]**
Number of patients	20	42	40	20	41	40
Age (years):						
Mean± SD	30.75±4.79	49.2±5.3	71.1±5.6	30.7±5.4	52.1±5.8	69.9±4.37
Range	{22-39}	{41-59}	{62-86}	{23-39}	{41-59}	{61-79}
Gender:						
Female	7 (35)	22 (52.4)	14 (35)	11 (55)	20 (48.7)	14 (35)
Male	13 (65)	20 (47.6)	26 (65)	9 (45)	21 (51.3)	26 (65)
Education :						
Illiterate	0 (0)	0 (0)	1 (2.5)	0 (0)	1 (2.4)	13 (32.5)
Less than high school	6 (30)	20 (47.6)	14 (35)	7 (35)	14 (34.1)	16 (40)
High school	10 (50)	16 (38.1)	17 (42.5)	8 (40)	17 (41.5)	9 (22.5)
Associate degree	2 (10)	3 (7.1)	5 (12.5)	5 (25)	6 (14.6)	2 (5)
Bachelor and beyond	4 (20)	3 (7.1)	3 (7.5)	0 (0)	3 (7.3)	0 (0)
Occupation						
Unemployed	9 (45)	22 (52.4)	15 (37.5)	11 (37.5)	25 (61)	14 (35)
Employed	11 (55)	5 (11.9)	0 (0)	9 (45)	15 (36.6)	0 (0)
Retired	0 (0)	15 (35.7)	25 (62.5)	0 (0)	1 (2.4)	26 (65)
Smoking Habit :						
Active smoker	7 (35)	23 (54.8)	17 (42.5)	10 (50)	24 (58.5)	18 (45)
Former smoker	6 (30)	7 (16.7)	8 (20)	1 (5)	6 (14.6)	7 (17.5)
Never smoked	7 (35)	12 (28.6)	15 (37.5)	9 (45)	11 (26.8)	15 (37.5)
Caffeine /day:						
No caffeine	5 (25)	5 (25)	4 (10)	3 (15)	6 (14.6)	7 (17.5)
1cup/day	3 (15)	3 (15)	18 (45)	7 (35)	19 (46.3)	12 (30)
2cups/day	9 (45)	9 (45)	14 (35)	7 (35)	11 (26.8)	17 (42.5)
3cups/day	2 (10)	2 (10)	3 (7.5)	3 (15)	5 (12.2)	3 (7.5)
More than 3cups/day	1 (5)	1 (5)	1 (2.5)	0 (0)	0 (0)	1 (2.5)

Diet for ESRD	2 (10)	4 (9.5)	4 (10)	5 (25)	7 (17.1)	8 (20)
Herbal use						
Using herbals	9 (45)	22 (52.4)	24 (60)	10 (45)	16 (39.0)	17 (42.5)
Not using herbals	11 (55)	20 (47.6)	16 (40)	10 (50)	25 (61.0)	23 (57.5)
Marital Status :						
Married	6 (30)	22 (52.4)	40 (100)	8 (40)	38 (92.7)	40 (100)
Single	14 (70)	5 (11.9)	0 (0)	12 (60)	3 (7.3)	0 (0)
Engaged	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Widow	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Divorced	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Performing exercise	12 (60)	21 (50)	18 (45)	12 (60)	18 (43.9)	20 (50)
Type of exercise						
Walking	7 (35)	17 (40.5)	13 (32.5)	7 (35)	11 (26.8)	15 (37.5)
Home activities	2 (10)	2 (4.75)	3 (7.5)	3 (15)	2 (4.8)	3 (7.5)
Work activities	3 (15)	2 (4.75)	2 (5)	2 (10)	2 (12.1)	2 (5)
Duration of exercise						
Less than 30 mins	5 (25)	18 (42.9)	14 (35.0)	6 (30)	15 (36.5)	15 (50)
More than 30 mins	7 (75)	3 (7.1)	4 (10.0)	6 (30)	3 (7.3)	5 (12.5)
Frequency per week						
3 times or more	3 (15)	10 (32.8)	6 (15.0)	3 (15)	10 (24.3)	8 (20)
Less than 3 times	9 (45)	11 (26.1)	12 (30.0)	9 (45)	8 (19.5)	12 (30.0)

1: Percent out of patients in mentioned group.

Patient's medical history

The medications of HD patient's in each group of the four studied groups are summarized in Tables (2) and (3**).**

Table-2: The most common medications (other than anemia medications) used by the study population

Patient's study group	**Intervention group (n=102)**			**Control group (n=101)**		
Group No.	**Group 1. N (%)[1]**	**Group 3. N (%)[1]**	**Group 5. N (%)[1]**	**Group 2. N (%)[1]**	**Group 4. N (%)[1]**	**Group 6. N (%)[1]**
Number of patients	20	42	40	20	41	40
CaCO3	18 (90)	41 (97.6)	40 (100)	20 (100)	41 (100)	40 (100)
Alfacalcidiol	18 (90)	41 (97.6)	40 (100)	20 (100)	41 (100)	39 (97.5)
Nifedipine	14 (70)	26 (61.9)	30 (75)	15 (75)	32 (78)	18 (45)
Amlodipine	1 (5)	11(26.2)	9 (22.5)	5 (25)	10 (24.4)	20 (50)
Frusemide	4 (20)	25 (59.5)	22 (55)	7 (35)	18 (43.9)	11 (27.5)
Enalapril	1 (5)	15 (35.7)	12 (30)	3 (15)	21 (51.2)	18 (45)
Candesartan	0 (0)	11 (26.6)	7 (17.5)	0 (0)	9 (22)	12 (30)
Bisoprolol	2 (10)	11 (26.6)	11 (27.5)	4 (20)	11 (26.8)	9 (22.5)
Atenolol	4 (20)	4 (9.5)	8 (20)	4 (20)	7 (17.1)	10 (25)
Carvedilol	0 (0)	3 (7.1)	2 (5)	0 (0)	3 (7.3)	9 (22.5)
Hydralazine	4 (20)	20(47.6)	14 (35)	4 (20)	14 (34.4)	14 (35)
Doxazocin	2 (10)	8 (19)	7 (17.5)	0 (0)	4 (9.8)	7 (17.5)
Methyldopa	2 (10)	4 (9.5)	5 (12.5)	1 (5)	8 (19.5)	8 (20)
S/c insulin	0 (0)	13 (31)	10 (25)	1 (5)	10 (24.4)	14 (35)
Aspirin	3 (15)	18 (42.9)	12 (30)	4 (20)	14 (34.1)	14 (35)
H2 blocker	7 (35)	15 (35.7)	22 (55)	11 (55)	24 (58.5)	22 (55)
PPI	4 (20)	19 (45.2)	13(32.5)	4 (20)	17(41.5)	13(32.5)
Statin	4 (20)	23 (54.8)	15 (37.5)	1 (5)	15 (36.6)	15 (37.5)
Sulfonylurea	0 (0)	6 (14.3)	4 (10)	1 (5)	8 (19.5)	4 (10)
Agents for neuropathy	0 (0)	11 (26.2)	7 (17.5)	0 (0)	6 (14.6)	11 (27.5)
Sevalamer	1 (5)	2 (4.8)	2 (5)	0 (0)	2 (4.9)	2 (5)
Nitrates	1 (5)	6 (14.3)	4 (10)	0 (0)	7 (17.1)	3 (7.5)
Antihistamine	4 (20)	22(52.4)	15(37.5)	0 (0)	20(48.8)	23 (57.5)
Others [2]	4 (20)	7 (16.7)	8 (20)	1(5)	6 (14.6)	8 (20)

1: Percent out of patients in mentioned group.2: Allopurinol, Alendronate Na, Gemfibrizoil, Multi vitamins, Tamsolucin, Warfarin; PPI, Proton Pump Inhibitor

Table-3: Medications used for the management of anemia in CKD patients recruited in the study

Patient's study group	Intervention group (n=102)			Control group (n=101)		
Group No.	**Group 1. N (%)[1]**	**Group 3. N (%)[1]**	**Group 5. N (%)[1]**	**Group 2. N (%)[1]**	**Group 4. N (%)[1]**	**Group 6. N (%)[1]**
Number of patients	20	42	40	20	41	40
Erythropoietin dose/ week:						
Not given	4 (20)	0 (0)	0 (0)	3 (15)	2 (4.9)	0 (0)
4000 IU/week	7 (35)	15 (35.7)	14 (35)	7 (35)	11 (26.8)	8 (20)
8000 IU/week	4 (20)	25 (59.5)	18 (45)	6 (30)	14 (34.1)	6 (15)
12000 IU/week	5 (25)	2 (4.8)	8 (20)	4 (20)	14 (34.1)	26 (65)
Iron sucrose (i.v):						
Not given	20 (100)	31 (73.8)	33 (82.5)	19 (95)	34 (82.9)	36 (90)
50 mg/week	0 (0)	0 (0)	0 (0)	0(0)	0 (0)	0 (0)
100 mg/session	0 (0)	11 (26.2)	5 (12.5)	0 (0)	3 (7.3)	4 (10)
Oral Ferrous gluconate	1 (5)	18 (42.9)	15(37.5)	6 (30)	20 (48.8)	22 (55)
Oral Folic acid	3 (15)	16 (38.1)	10 (25)	6 (30)	27 (65.9)	12 (30)
Quantity of blood transfusion one month before enrolment:						
No blood transfusion	14 (70)	23 (54.8)	27 (67.5)	13 (65)	27 (65.9)	38 (95)
One unit	2 (10)	17 (40.5)	8 (20)	5 (25)	12 (29.3)	1 (2.5)
Two units	3 (15)	1 (2.4)	4(10)	1 (5)	1 (2.4)	1 (2.5)
More than 2 units	1 (5)	1 (2.4)	1 (2.5)	1(5)	1 (2.4)	0 (0)
Quantity of blood transfusion one month at enrolment:						
No blood transfusion	16 (80)	42(100)	34(85)	15 (75)	36 (87.8)	39 (97.5)
One unit	4 (20)	0 (0)	5 (12.5)	4 (20)	3 (7.3)	5 (2.5)
Two units	0 (0)	0 (0)	1 (2.5)	1 (5)	2 (4.9)	0 (0)
More than 2 units	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Patient management phase						
Correction phase	14 (70)	27 (64.3)	25 (62.5)	14 (70)	31 (75.6)	17 (42.5)
Maintenance phase	6 (30)	15 (35.7)	15 (25)	6 (30)	10 (24.4)	23 (57.5)

1: Percent out of patients in mentioned group.

Baseline Clinical Characteristics

The details of clinical characteristics of patients are shown in tables 4 and 5.

Table-4: Blood chemistry baseline characteristics for the participants (n=203)

Patient's study group	Intervention group			Control group		
Group No.	**Group 1**	**Group 3**	**Group 5**	**Group 2**	**Group 4**	**Group 6**
Number of patients	20	42	40	20	41	40
BUN (mg/dl) Mean± SD	65.5±13.2	71.3±18.6	64.6±14.3	67.9±14.7	69.8±14.6	63.9±17.5
Serum Creatinine (mg/dL) Mean± SD	10.9±2.01	9.7±2.17	10.4±2.8	10.8±2.6	10.3±2.7	5.2±1.85
CrCl (ml/min) Mean± SD	5.1±0.97	5.4±1.97	5.5±2.02	5.3±1.61	5.7±2.2	4.9±0.89
Albumin (g/dL) Mean± SD	39.7±6.7	38.4±2.6	38.1±1.9	39.2±3.06	38.8±2.8	38.6±1.97
Na (mEq/L) Mean± SD	138±20.9	138±21.8	133±21.2	138±21.7	134±21.0	134±22.2
K (mEq/L) Mean± SD	4.7±1.23	4.83±1.05	4.7±1.08	4.69±0.89	4.67±0.91	4.3±1.18
Ca (mg/dl) Mean± SD	8.6±0.81	8.85±0.73	8.6±0.67	8.7±0.61	8.7±0.69	8.9±0.88
PO4 (mg/dl) Mean± SD	4.9±0.8	4.91±0.83	4.92±0.81	4.7±0.52	4.9±0.81	4.52±0.71

Table-5: Complete blood count and Iron indices for the participants in the study

Patient's study group	Intervention group	Control group

Group No.	Group 1	Group 3	Group 5	Group 2	Group 4	Group 6
Patient's number	20	42	40	20	41	40
Hemoglobin (g/dL) Mean± SD	8.8±2.2	10.1±1.9	9.75±1.48	9.2±2.4	9.3±2.06	9.95±1.98
Hematocrit % Mean± SD	27±6.02	30.8±5.7	29.7±4.62	28±7.3	28.6±6.1	29.3±4.12
MCV Mean± SD	84±5.6	86.2±6.94	87.5±4.59	85.5±5.55	86.6±5.47	87.3±4.19
MCHC Mean± SD	32.3±1.59	32.9±1.37	32.7±1.42	32.5±1.25	33.1±1.46	31.7±1.49
MCH Mean± SD	27.5±3.2	28.7±2.53	28.8±1.99	28.2±1.85	28.4±1.93	28.7±1.93
RBCs Mean± SD	3.1±0.43	3.4±0.73	3.41±0.53	3.2±0.83	3.2±0.66	3.45±0.58
RDW-CV Mean± SD	14.3±0.98	14.7±1.29	15.1±1.98	14.6±1.48	14.7±1.43	15.2±1.38
Platelets Mean± SD	215±45.9	213±55.2	209±48.1	192±42.2	208±52.7	221±65.4
WBCs Mean± SD	6.01±1.7	6.65±1.51	6.7±2.03	5.8±1.18	6.1±1.7	6.6±1.53
Iron (µg/dL) Mean± SD	52.3±17.1	60.9±26.8	59.2±23.8	64.9±41.3	57.8±31.59	54.1±19.7
Ferritin(ng/mL) Mean± SD	159±99.2	156±131	161±88	170±105	119±67.7	149±90
TIBC (µg/dL) Mean± SD	262±45.4	282±64.2	280±64	278±68.7	266±74.2	265±54
TSAT % Mean± SD	19.8±5.66	21±6.39	23.5±11.3	22.5±9.09	23.6±6.6	19.8±5.66

Treatment Related Problems (TRPs) identified among CKD patients

The main identified anemia related TRPs are shown in Table (6-7). The total number of TRPs identified in the three interventional groups was (493) problems related to anemia with a mean of 4.8±1.81 TRP per patient. In the control group, the total number of TRPs identified was 302 with a mean of 3±1.3 TRP per patient. The most frequent TRP observed in the interventional study sample was efficacy drug related problem (n=269, 54.5%) followed by untreated conditions that require drug therapy (n=162, 32.8%). The most commonly involved drug in TRPs related to anemia in the three interventional groups was I.V iron sucrose (n=94, 19%). Individually, I.V iron sucrose for the management of low ferritin level formed 55% of the category "More effective drug is available or recommended". ESA related problems TRPs under the title "Efficacy dosage regimen issues" accounted to about 18% of total TRPs. The TRP titled "A need for additional diagnostic test" accounted 11% for the total TRPs in the three interventional groups.

Clinical Pharmacist Role

Types of Interventions Provided by the Pharmacist during the Study

The TRPs identified in the intervention groups during the study were resolved through 383 pharmacist's interventions submitted to the physicians by written pharmacist consult notes. All submitted consult notes had the agreement on implementation. The Physicians were approached to add or start drug therapy in 45% of recommendations, to increase or decrease ESA dose in 24.2% of interventions, , to perform further lab tests to evaluate B12 and serum folate level in 13.8% of recommendations, and to withhold ESA for 2 weeks in 2.3% of interventions. B12 deficient patients were treated with 1000 mcg of intramuscular cyanocobalamin weekly for the first month and then monthly for two consecutive months. All injections were given in the deltoid muscle prior to the initiation of the hemodialysis session. While folate deficient patients were prescribed oral folic acid tablets 5 mg/day, which is the only preparation available in the RMS.

Patient Management Phase

At the beginning of the study, only 36 out of 102 (35%) patients in the 3 intervention groups were in the maintenance phase {Hb is within target (10-12 g/dl)}. This was not significantly different from the

control group, in which 24 of 101 (24%) patients had their Hb at goal (p=0.091). At the end of the study, Hb was at target significantly more in patients in the intervention group89 out of 102 (87.2%) than in the control group 37 out of 101 (36.6%) (p = 0.02).

Clinical Outcome of Pharmacist interventions

Parameters related to anemia management (Hb, Hct, ferritin, and TSat) are shown in the form of tables in this section, which compare the outcome of the pharmacist intervention groups with physician control group in the same age group, except for B12 level and serum folate level which were only performed in the intervention groups as a part of the clinical pharmacist interventions.

Table-6: The distribution of anemia related TRPs among the 3 Intervention groups of the study (n=102)

TRP category	TRP	Drug or Condition involved	Interventional Study Group					
			Group 1 Patient's No (20)		Group 3 Patient's No (42)		Group 5 Patient's No (40)	
			Number of TRPs (92)		Number of TRPs (201)		Number of TRPs (200)	
			N (%)[1]	N (%)[2]	N(%)[1]	N(%)[2]	N(%)[1]	N(%)[2]
1. Unnecessary drug therapy	c) The patient treatment should be stepped down/withhold for 2 weeks	ESA	0 (0)	0 (0)	4 (1.9)	4 (0.81)	5 (2.5)	5 (1)
2- Untreated conditions	a) Untreated conditions that require drug therapy*	1-Low ferritin level and low TSat 2-Low /border line B12 level 3-Low serum folate level	14 (15.2) 8 (8.7) 8 (8.7)	14 (2.8) 8 (1.6) 8 (1.6)	29 (14.4) 22 (10.9) 17 (8.4)	29 (5) 22 (4.4) 17 (3.4)	27 (13.5) 22 (11) 15 (7.5)	27(5.4) 22 (4.4) 15 (3)
3- Efficacy drug related problems	a) More effective drug is available/recommended	1- I.V iron sucrose (supplemental dose or maintenance dose) 2- I.V B12 3- Oral folic acid	20 (21.7) 8 (8.7) 8 (8.7)	20 (4) 8 (1.6) 8 (1.6)	36 (17.9) 22 (10.9) 12 (6)	36 (17.7) 22 (4.4) 12 (2.4)	38 (19) 22 (11) 10 (5)	38 (7.7) 22 (4.4) 10 (2)
	b) Efficacy dosage regimen issues	Weekly ESA dose	18 (19.6)	18 (36)	36 (17.9)	36 (17.7)	39 (19.5)	39 (7.9)
7- Miscellaneous	c) A need for additional diagnostic test	B12 level and serum folate	8 (8.7)	8 (1.6)	23 (11.4)	23 (4.6)	22 (11)	22 (4.4)

ESA, Erythropiotein Stimulating Agent; I.V, Intravenous; TRP, Therapeutic Related Problem; TSat, Transferrin Saturation

1: Percent out of number TRPs in mentioned group.

2: Percent out of total number of TRPs.

* B12 level and serum folate level are obtained by the pharmacist recommendation only for the interventional groups

Table-7: The distribution of anemia related TRPs among the 3 control groups of the study (n=101)

			Control Study Group

TRP category	TRP	Drug or Condition involved	Group 1 Patient's No (20)		Group 3 Patient's No (41)		Group 5 Patient's No (40)	
			Number of TRPs (60)		Number of TRPs (119)		Number of TRPs (123)	
			N (%)[1]	N (%)[2]	N(%)[1]	N(%)[2]	N(%)[1]	N(%)[2]
1. Unnecessary drug therapy	c) The patient treatment should be stepped down/withhold for 2 weeks	ESA	2 (3.3)	2 (0.66)	2 (3)	2 (0.66)	1 (0.8)	1 (0.33)
2- Untreated conditions	a) Untreated conditions that require drug therapy	Low ferritin level and low Tsat	15 (25)	15 (4.9)	27 (24)	27 (8.94)	29 (23.5)	29 (9.6)
3- Efficacy drug related problems	c) More effective drug is available/recommended	I.V iron sucrose (supplemental dose or maintenance dose)	18 (30)	18 (5.9)	35 (30)	35 (11.5)	37 (30)	37 (12.2)
	d) Efficacy dosage regimen issues	Weekly ESA dose	16 (26)	16 (5.2)	34 (30)	34 (11.2)	36 (29.2)	36 (11.9)
7- Miscellaneous	c) A need for additional diagnostic test	B12 level and serum folate	9 (15)	9 (2.9)	21 (19)	21 (6.9)	20 (16.2)	20 (6.6)

ESA, Erythropiotein Stimulating Agent; I.V, Intravenous; TRP, Therapeutic Related Problem; TSat,Transferrin Saturation
1: Percent out of number TRPs in mentioned group.
2: Percent out of total number of TRPs.

Table-8: Types of interventions provided by the pharmacist during the study

Type of Intervention	Pharmacist's action (%)[a]	Type of Intervention	Pharmacist's action (%)[a]
Add drug therapy	Administer i.v Cyanocobalamin 1mg/ml regimen for 3 months (13)	**Perform specific Lab tests**	Request B12 level and serum folate (13.8)
	Administer oral folic acid 5mg/day (8)	**Stop drug**	Withhold ESA for 2 weeks (2.3)
Increase drug dose	Increase weekly ESA dose according to patient weight and Hb (15.6)	**Education regarding medication**	Providing drug information about ESA, Iron Sucrose, Cyanocobalamin, and Folic Acid (11.2)
Decrease drug dose	Decrease weekly ESA dose according to patient weight and Hb (8.6)	**Education regarding anemia** .	Providing information on renal anemia to physicians and nurses (3.5)

[a] percentage out of 383 interventions. ESA, Erythropiotein Stimulating Agent; I.V, Intravenous; Hb, Hemoglobin

Table-9: Frequency and percentages of hemoglobin goal achievement among both study arms at 3 months compared to baseline

		Intervention n= 102 (%)[1]	Control n= 101 (%)[1]	*p*-value *
Patients who are at target Hb **at baseline:** Hb 10-12 g/dl	Maintenance phase (at goal)	36 (35.2%)	24 (24%)	0.091
		Intervention n= 102 (%)[1]	**Control n= 101 (%)[1]**	
Patients who are at target Hb **at the end of study:** Hb 10-12 g/dl	Maintenance phase (at goal)	89 (87.2%)	37 (36.6%)	0.02

1: Percent out of patients in mentioned group. Hb, Hemoglobin
**p*-value obtained by Chi-Square test for difference between end of study and baseline, statistically significant if *p* value<0.05

Interventional Arm vs Control Arm

A total of 203 patients, 102 in the pharmacist-managed group and 101 in the usual care group, were

included in the study. Of the anemia monitoring parameters, the pharmacist- managed group demonstrated superior performance results for hemoglobin goal achievement at the end of the study (achieved in 87.2% of patients vs. 36.6% in the usual care group, p= 0.02) and no difference for baseline hemoglobin (p =0.133).

For the iron-monitoring parameters, no significant differences were observed between the two arms for the both parameters Ferritin and TSat at the beginning of the study, the p value for Ferritin and TSat at baseline for the intervention and control group was 0.176 and 0.35 respectively. At the end of the study the mean for Ferritin and TSat in the interventional arm was 376.8 and 34.7 respectively, whereas in the control arm the mean was143.8 and 19.02 respectively with a statistically significant p value between the two study arms (p value for Ferritin =0.002, p value for TSat =0.002). Table (10) shows the results of anemia management parameters among the two study arms.

Table-10: Anemia monitoring parameters between interventional arm and control arm

Parameter	**Arm**	**Baseline, Mean ± SD**	**End of study, Mean ± SD**	**Change Mean ± SD**	***p*-value * (within each group)**
Hb	**Interventional**	**9.7±1.87**	**11.54±0.5**	**1.84± 0.84**	**0.002**
	Control	**9.2±2.3**	**9.98±1.49**	**16.4± 1.67**	**0.071**
***p*-value ** (between the two arms)at baseline**=0.133 ***p* -value *** (between the two arms)at end of the study**= 0.002					
Pararmeter	**Arm**	**Baseline, Mean ± SD**	**End of study, Mean ± SD**	**Change Mean ± SD**	***p*-value * (within each group)**
Hct	**Interventional**	29.6±5.5	34.9±1.6	5.3± 2.34	0.002
	Control	28.1±7	30.46±4.5	2.36±1.84	0.068
***p*-value ** (between the two arms) at baseline**=0.119 ***p* -value *** (between the two arms)at end of the study**=0.002					
Parameter	**Arm**	**Baseline, Mean ± SD**	**End of study, Mean ± SD**	**Change Mean ± SD**	***p*-value * (within each group)**
Ferritin	**Interventional**	159±108.7	376.8±75.5	217.8± 91.32	0.002
	Control	140±87.5	140.8±55.06	0.8±1.24	0.688
***p*-value ** (between the two arms) at baseline**=0.176 ***p* -value *** (between the two arms) at end of the study**= 0.002					
Parameter	**Arm**	**Baseline, Mean ± SD**	**End of study, Mean ± SD**	**Change Mean ± SD**	***p*-value * (within each group)**
TSat	**Interventional**	21.8±8.9	34.7±6.23	12.9± 6.16	0.002
	Control	23.3±13.9	21.2±2.15	-2.1±3.82	0.121
***p*-value ** (between the two arms) at baseline**=0.35 ***p* -value *** (between the two arms)at end of the study**= 0.002					

***p* value obtained by independent t-test statistically, significant if p value<0.05,
***p*-value *and* ****p* –value obtained by ANOVA test for difference between end of study and baseline, statistically significant if p value<0.05

Financial Outcome of Pharmacist interventions

During the study period (3 months), the same drugs were used in the management of anemia between the two study arms, with the exception of parenteral vitamin B12 which was used as one of the interventions in pharmacist care groups. Epoetin alfa is the most expensive drug used during the study, the price of (Eprex®) vial of 4000 IU according to the last tender of the JRMS was 12.30 JD for each vial. The average amount of epoetin alfa vials in the form of (Eprex® 4000 IU) used in the pharmacist control group (24.65 vial/patient), resulting in considerable cost savings. Table (11) compares the quantity and prices between the drugs used in the study among the two arms.

Table-11: The quantity and prices of the drugs used in the management of anemia in the study among the two arms.

Study Arm	**Total vials of Epotein α (Eprex®) 4000 IU used during the study**	**Mean and SD of Epotein α (Eprex®) 4000 vials IU/ patient consumption**	**Cost of Epotein α (Eprex®) 4000 IU, Unit price = 12.3 JD/vial of 4000 IU**	**Mean and SD of Epotein α (Eprex®) 4000 vials IU cost**
Interventional **N = 102**	1610	15.7±5.8	19803 JD	194.1±72.1
Control **N = 101**	2288	24.7±8.05	28142.4 JD	307.8±94.6
***p* value of consumption = 0.002, ***p*value of cost = 0.002**				
Study Arm	**Total vials of iron sucrose (Venofer®) 100 IU used during the study**	**Mean and SD of iron sucrose (Venofer®) vials 100 IU/ patient consumption**	**Cost iron sucrose of (Venofer®) 100 IU, Unit price = 2.55 JD/vial of 100 IU**	**Mean and SD of iron sucrose (Venofer®) 100 IU cost**
Interventional **N = 102**	1342	13.1±4.7	3422.1 JD	33.25±3.44
Control **N = 101**	340	3.3±1.6	867 JD	8.42±3.67
***p* value of consumption = 0.002, ***p*value of cost = 0.002**				
Study Arm	**Total tablets of folic acid (Vifolin®) 5 mg**	**Mean and SD folic acid (Vifolin®)5mg consumption**	**Cost of folic acid (Vifolin®) 5 mg Unit price = 0.007 JD/tab of 5 mg**	**Mean and SD of folic acid (Vifolin®) 5 mg cost**
Interventional **N = 102**	5130	49.9±44.9	35.91 JD	0.35±0.93
Control **N = 101**	2790	27.6±41.7	19.53 JD	0.189±0.24
***p* value of consumption = 0.002, ***p* value of cost** = *0.002*				
Study Arm	**Total ampules of vitamin B12 1000mg**	**Mean and SD Total ampules of vitamin B12 1000mg consumption**	**Cost of Total ampules of vitamin B12 1000 mg Unit price = 0.14 JD/amp of 1000 mg**	**Mean and SD of vitamin B12 1000 mg cost**
Interventional **N = 102**	318	3.12±3.01	44.52	0.43±0.52

Study Arm	**Total cost of the drugs used in the management of anemia in JD**	**Mean±SD**	**Savings in JD**	***p*- value**
Interventional **N = 102**	23305.53	229.6±78.2	5723.4	0.002
Control **N = 101**	29028.93	312.7±98.4		

*p and**p-value obtained by ANOVA test, statistically significant if p value<0.05.

DISCUSSION

Assessment and Resolution of Treatment Related Problems

To manage TRPs, each HD unit should have a clinical pharmacist as a member of the health care team to provide medical care to HD patients. Services administered by a clinical pharmacist have been shown to be cost-effective and associated with improvement of the quality of life [15].

The total number of TRPs identified in the three interventional groups was (493) problems related to anemia with a mean of 4.8±1.81 TRP per patient resolved through 383 pharmacist's interventions submitted to the Physicians by written pharmacist consult note. The most frequent TRP observed in the interventional study sample was efficacy drug related problem (n=269, 54.5%) followed by untreated conditions that require drug therapy (n=162, 32.8%). The most commonly involved drug in TRPs related to anemia in the three interventional groups was I.V iron sucrose (n=94, 19%). Individually, I.V iron sucrose for the management of low ferritin level formed 55% of the category "More effective drug is available or recommended". ESA related problems TRPs under the title "Efficacy dosage regimen issues" accounted to about 18% of total TRPs. A study by Valderrabano *et al.* found that common mistakes in ESA prescribing include premature dosage increases, a starting dosage that is too high, and changing dosages by too large a margin [16]. In another study the most prevalent drug related problem regarding ESA was" Safety dosage

regimen issues" (69%). The study revealed that ESA doses and I.V iron were not administered and monitored according to the recommendations on target limits for patients receiving ESA [17].

Clinical Outcome

According to the RMS guideline for the management of anemia in HD patients, the therapeutic targets which include Hb 10-12 g/dl, Hct 30%-36%, ferritin level > 200 ng/ml, and TSat >20% were employed. And clinical pharmacist in this study made recommendations to nephrologists to check Hb concentration, iron status, vitamin B12 level and serum folate level based on this targets. Accordingly, pharmacist consulted physicians to change the dose of epotein α, give I.V iron sucrose when iron deficiency was present, administer I.V cyanocobalamin in low /border line level of vitamin B12 patients and prescribe oral folic acid in patients with low serum folate.

Achievement of hemoglobin goal levels in the current study may be attributed in part to better management of iron deficiency, low B12 level, and low serum folate. These are known causes for erythropoietin resistance [18]. A previous study showed that a large number of patients with low hemoglobin levels in the pre-intervention phase were also iron deficient, and most of these patients achieved target hemoglobin after iron administration [19].

Hemoglobin and Hematocrit

The results showed that decision making by clinical pharmacist based on laboratory results and application of the RMS guideline in managing anemia has an excellent impact on achieving target goal of Hb and Hct concentrations among HD patients in the interventional arm compared with the control arm. Since there was a significant increase in the number of patients who achieved target Hb and Hct at the end of the study (87.2% of pharmacist managed patients vs. 36.6% in the usual care group, p = 0.02). In a retrospective study, it was found that the pharmacist-administered anemia protocol was as effective as physician management [20]**.** Another study reported that involvement of pharmacists in the management of anemia in HD patients increased the number of patients with optimal hemoglobin levels within 2 months: 10-12g/dl [21]. In this study, pharmacists were able to check blood parameters, and decide the dose of ESA.

Ferritin and Transferrin Saturation

In our study, iron status in the interventional arm was monitored in conjunction with blood parameters in HD patients to ensure that patients have adequate iron stores when starting ESA therapy. Iron administration was initiated simultaneously with ESA treatment. Parenteral iron sucrose was administered as a supplemental dose to replenish diminished iron stores (i.e., serum ferritin <100 ng/mL or TSAT <20%) or as a maintenance dose (i.e., serum ferritin >200 ng/mL or TSat >20%).

The usefulness of iron supplementation does not only contributes to patients with iron deficiency but iron supplementation can prevent depletion of iron stores during ESA therapy, achieve and keep target Hb concentrations [22].

For the iron-monitoring parameters, the interventional arm had superior results for ferritin and TSat. These two greatly improved at the end of the study. At the end of the study the mean for Ferritin and TSat in the interventional arm were 376.8 ng/mL and 34.7% respectively, whereas in the control arm the means were 143.8 ng/mL and 19.02 % respectively with a statistically significant p value between the two study arms (p value for Ferritin =0.002, p value for TSat =0.002)**.**

Higher rates of iron monitoring and management of iron deficiencies based on laboratory results in our study contributed not only to increase the number of patients who achieved target Hb, but may have also lead to the marked lower ESA consumptions in the interventional arm**.**

Vitamin B12 Level and Serum Folate Level

B12 level and serum folate level were only performed in the interventional arm as a part of the clinical pharmacist interventions. Screening began with measurement of serum vitamin B12 concentrations and plasma folate level. The percent of patients with vitamin B12 deficiency was 50.9% (52/102), while it was 39% (40/102) for folate deficiency.

At the start of the study, the mean value for B12 level and serum folate level was 111.7 pg/ml and 3.1 ng/ml respectively, while at the end of the study, the mean value for B12 level and serum folate level was 385 pg/ml and 7.4 ng/ml respectively with a statistically significant p value (0.002 for both parameters). In a study by Saifan *et al.* intramuscular vitamin B12 supplementation resulted in a reduction in the average dose of ESA administration and keeping a stable Hb level [23].

Financial Outcome

Erythropoietin-stimulating agents (ESAs) are among the costliest drug therapies in the pharmacy budget at healthcare institutions. Efforts by pharmacists to develop and implement institutional protocols or guidelines for ESA use can have economic benefits as well as improve clinical outcomes. In this study, the clinical pharmacist followed RMS guideline for the use of epotein α and iron sucrose with the administration of I.V vitamin B12 and oral folic acid for the management of anemia in HD patients.

Patients in the pharmacist-managed group used less epotein α during the 3-month period, leading to a savings of 5723.4 JD for the total drug expenditures.

The average amount of epotein α vials in the form of (Eprex® 4000 IU) used in the pharmacist care group during the study was (15.7 vial/patient) which is lower than that in the conventional care group (24.65 vial/patient). This results in significant saving (P = 0.002). In a Japanese study; the pharmacist intervention was shown to reduce the monthly costs of erythropoietin from 1.86 to 1.37 million Japanese yen (the equivalent to 22600 USD and 16600 USD) in 9 months of the year 2002 [24].

CONCLUSIONS

- Patients managed by a clinical pharmacy anemia service had better clinical outcomes, and lower medication utilization compared with patients receiving usual care.
- Clinical pharmacists can positively contribute to the care of ESRD patients and reduce the gaps in current patient care.
- On a renal dialysis unit, the partnership developed between the patient and pharmacist is advantageous because it creates a supportive environment, encouraging patients to be confident to discuss their experiences or concerns about the medicines they are taking and their disease progression

RECOMMENDATIONS

It is recommended that clinical pharmacists should actively participate in management of TRPs in HD patients. Many TRPs have been identified in the HD units; including untreated conditions, treatment failure, inappropriate dosage, under or over dose, incorrect administration, and patient non- adherence which might be attributed to the lack of multidisciplinary services, providing such services by a teams of physicians, nurses, dieticians, and clinical pharmacists share the goal of preventing TRP.

REFERENCES

1. Deng, Y., Li, N., Wu, Y., Wang, M., Yang, S., Zheng, Y., ... & Gao, J. (2021). Global, Regional, and National Burden of Diabetes-Related Chronic Kidney Disease from 1990 to 2019. *Frontiers in endocrinology*, *12*, 809.
2. The MEP Group for Kidney Health. (2010). European Kidney Health Alliance: Chronic Kidney Disease and Diabetes – A Major Threat to Europe's Health Retrieved from European Kidney Health Alliance web site, http://www.ekha.eu/usr_img/newsroom/2010/10_03_10.pdf.
3. Tarawneh, M., & Al-Qaisi, S. (2012). National Registry of End Stage Renal Disease, Annual Report 2009-2010, Non Communicable Disease Directorate, The Hashemite Kingdom of Jordan Ministry of Health, Amman, Jordan.
4. Eknoyan, G., Lameire, N., Eckardt, K., Kasiske, B., Wheeler, D., Levin, A., ... & Levey, A. S. (2013). KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int*, *3*(1), 5-14.
5. Bolton, W. K. (1998). The role of the nephrologist in ESRD/Pre-ESRD care: a collaborative approach. *Journal of the American Society of Nephrology: JASN*, *9*(12 Suppl), S90-5.
6. Silva, G. B. D., Oliveira, J. G. R. D., Oliveira, M. R. B. D., Vieira, L. J. E. D. S., & Dias, E. R. (2018). Global costs attributed to chronic kidney disease: a systematic review. *Revista da Associação Médica Brasileira*, *64*, 1108-1116.
7. Charles, C., & Ferris, A. H. (2020). Chronic kidney disease. *Prim Care-Clin Off Pract*, *47*(4), 585-95.
8. Rysz, J., Gluba-Brzózka, A., Franczyk, B., Jabłonowski, Z., & Ciałkowska-Rysz, A. (2017). Novel biomarkers in the diagnosis of chronic kidney disease and the prediction of its outcome. *International journal of molecular sciences*, *18*(8), 1702.
9. Sato, Y., Fujimoto, S., Konta, T., Iseki, K., Moriyama, T., Yamagata, K., ... & Watanabe, T. (2018). Anemia as a risk factor for all-cause mortality: obscure synergic effect of chronic kidney disease. *Clinical and experimental nephrology*, *22*(2), 388-394.
10. Palaka, E., Grandy, S., van Haalen, H., McEwan, P., & Darlington, O. (2020). The impact of CKD anaemia on patients: incidence, risk factors, and clinical outcomes—a systematic literature review. *International journal of nephrology*, *2020*.
11. Kiss, Z., Elliott, S., Jedynasty, K., Tesar, V., & Szegedi, J. (2010). Discovery and basic pharmacology of erythropoiesis-stimulating agents (ESAs), including the hyperglycosylated ESA, darbepoetin alfa: an update of the rationale and clinical impact. *European journal of clinical pharmacology*, *66*(4), 331-340.
12. Del Vecchio, L., & Minutolo, R. (2021). ESA, Iron Therapy and New Drugs: Are There New Perspectives in the Treatment of Anaemia?. *Journal of Clinical Medicine*, *10*(4), 839.
13. Thomson, C., Gunther, M., & Macek, P. (2019). Clinical Pharmacists in Correctional Facilities: A Literature Review and Future Directions. *Journal of Correctional Health Care*, *25*(3), 201-213.
14. AbuRuz, S. M., Bulatova, N. R., & Yousef, A. M. (2006). Validation of a comprehensive classification tool for treatment-related problems. *Pharmacy World and Science*, *28*(4), 222-232.
15. Pai, A. B., Cardone, K. E., Manley, H. J., Peter, W. L. S., Shaffer, R., Somers, M., & Mehrotra, R. (2013). Medication reconciliation and therapy management in dialysis-dependent patients: need

for a systematic approach. *Clinical Journal of the American Society of Nephrology*, *8*(11), 1988-1999.

16. Valderrábano, F., Hörl, W. H., Macdougall, I. C., Rossert, J., Rutkowski, B., & Wauters, J. P. (2003). PRE-dialysis survey on anaemia management. *Nephrology Dialysis Transplantation*, *18*(1), 89-100.
17. Zhang, H., Ho, Y. F., Che, C. T., Lin, Z. X., Leung, C., & Chan, L. S. (2012). Topical herbal application as an adjuvant treatment for chronic kidney disease–a systematic review of randomized controlled clinical trials. *Journal of advanced nursing*, *68*(8), 1679-1691.
18. Ramanath, V., Gupta, D., Jain, J., Chaudhary, K., & Nistala, R. (2012). Anemia and chronic kidney disease: making sense of the recent trials. *Reviews on recent clinical trials*, *7*(3), 187-196.
19. Hundert, J. S., & Singh, A. K. (2014). Anemia and Disorders of Hemostasis in Chronic Kidney. *Management of Chronic Kidney Disease: A Clinician's Guide*, 205.
20. To, L. L., Stoner, C. P., Stolley, S. N., Buenviaje, J. D., & Ziegler, W. (2001). Effectiveness of a pharmacist-implemented anemia management protocol in an outpatient hemodialysis unit. *American journal of health-system pharmacy*, *58*(21), 2061-2065.
21. Ohnishi, J., Miyake, A., Kuwatsuka, K., Onoue, Y., Lee, M., Koyama, T., ... & Kitamura, Y. (2011). Effect of pharmacist management on serum hemoglobin levels with renal anemia in hemodialysis outpatients. *Biological and Pharmaceutical Bulletin*, *34*(10), 1609-1612.
22. Del Vecchio, L., & Minutolo, R. (2021). ESA, Iron Therapy and New Drugs: Are There New Perspectives in the Treatment of Anaemia?. *Journal of Clinical Medicine*, *10*(4), 839.
23. Saifan, C., Samarneh, M., Shtaynberg, N., Nasr, R., El-Charabaty, E., & El-Sayegh, S. (2013). Treatment of confirmed B12 deficiency in hemodialysis patients improves Epogen® requirements. *International journal of nephrology and renovascular disease*, *6*, 89.
24. Kimura, T., Arai, M., Masuda, H., & Kawabata, A. (2004). Impact of a pharmacist-implemented anemia management in outpatients with end-stage renal disease in Japan. *Biological and Pharmaceutical Bulletin*, *27*(11), 1831-1833.