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Role of Clinical Pharmacist in Identification and Resolution of Drug-Related Problems in Hemodialysis Patients

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Abstract

Chronic kidney disease (CKD) is kidney impairment signified by a glomerular filtration rate (GFR) of less than 60 mL/min/1.73m² for 3 months or more. CKD can eventually lead to end-stage renal disease (ESRD); representing the last stage of CKD when renal replacement therapy (RRT) becomes necessary. The prevalence of CKD and ESRD is increasing continuously due to the dramatic growth in the prevalence of two main causes of ESRD; diabetes mellitus (DM) and hypertension, hence, ESRD represents a global concern. There are three modalities of RRT available for ESRD patients: transplantation, hemodialysis (HD), and peritoneal dialysis (PD). Although transplantation is the best treatment as it improves patients' quality of life and reduces expenses, HD represents the main modality of RRT for ESRD patients. As HD patients suffer many medical conditions, they are managed by different prescribers, an average HD patient is on 10-12 different medications per day, leading to higher exposure to drug-related problems (DRPs). Many studies worldwide estimated the rate of DRPs in HD patients to be high, studies identifying the rate and types of DRPs are to be found in the literature, but there is a scarcity of such studies regarding the Egyptian HD population.

Keywords

CKD, ESRD, HD, drug-related problems, medication-related problems

Introduction

Patients with CKD usually have several concurrent comorbidities such as hypertension, diabetes, and cardiovascular diseases. Patients with advanced CKD often suffer from anemia as well as bone and mineral metabolism abnormalities, in addition to fluid and electrolyte abnormalities. As a consequence, an average HD patient uses 10-12 medications [1].

In addition to the multiple comorbidities and the use of many medications, CKD patients also suffer from the fragmentation of care; they receive medication prescriptions from nephrologists in the dialysis center, as well as primary care physicians and specialty physicians such as endocrinologists or cardiologists. As a result of these factors; dialysis patients are highly susceptible to developing medication-related problems (MRPs) [1].

A very common term used when addressing dialysis patients is "polypharmacy", the term "polypharmacy" has many definitions, but generally, it usually refers to the regular use of four or more medications by older patients, or excessive drug use/drug therapy that is not necessary ^{2, 3}. Polypharmacy with both of the previous definitions is very often identified in dialysis patients, and when patients' medication lists are reviewed and untreated conditions are identified, patients are prescribed additional medications, consequently, the problem is exacerbated. Polypharmacy can increase the risk of drug-drug interactions and adverse effects, however, the reduction of polypharmacy is not an adequate goal for dialysis patients, instead, health care providers should make

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it a priority to ensure that patients are receiving appropriate, safe, effective, and convenient medication therapy [4].

The identification, resolution, and prevention of DRPs, at times called MRPs, are of the main processes of pharmaceutical care. Actions aimed at improving the use of medications help to correct or prevent DRPs, such as interactions and adverse drug reactions (ADRs)[5].

Numerous definitions and classification systems for "DRPs" and their synonyms are to be found in the literature ⁵⁻¹²; as there is no consensus on the structure of classification systems of DRPs for different healthcare settings [12].

Drug-related problems are usually defined as an event involving drug treatment that causes an actual or potential interference with the achievement of optimal outcomes desired for the patients ⁶, " medication-related problems" and " treatment-related problems" are comparable terms used by researchers to address problems with patients' medication therapy or patient treatment [13],[14].

DRPs in developed countries:

In 1997, Grabe et al. published their study evaluating DRPs in an outpatient HD unit and the impact of clinical pharmacist's participation in the unit. The authors conducted a thorough medication review for each patient through examination of medical records and computerized medication profiles, a clinical

pharmacist assessed the data for the Presence of DRPs. The authors identified 126 DRPs in over one month and 102 interventions were made. The most common DRP was drug interactions accounting for 27.5% of all identified DRPs. The study concluded that the inclusion of a clinical pharmacist in the HD unit led to the detection of various DRPs and numerous interventions, the majority of the interventions were significant and likely led to better outcomes [15].

In a study conducted by Manley et al. to assess types and frequency of MRPs in ambulatory HD patients, the participants were chosen by random selection and enrolled for monthly pharmaceutical care visits to identify MRPs, the authors found that the overall MRP frequency was 0.68 ± 0.46 per patient each month, drug dosing problems accounted for 33.5% of MRPs, adverse drug reactions accounted for 20.7%, and indications without treatment for 13.5% [16].

In another study by Manley et al. aiming to assess factors associated with MRPs in HD patients, MRPs were identified in 97.7% of the patients (n=133 patients) after review of patients' medical records, the authors identified a total of 475 MRPs with an average of 3.6 ± 1.8 MRP per patient. The authors found a positive correlation between the prevalence of MRPs and the number of comorbidities per patient (P < 0.001), more MRPs were identified in patients with DM compared to patients without it (303 vs. 172 respectively). The most frequently identified MRPs were "drug use without indication", "problems with laboratory tests", "indications without drug use", and "dosing errors" accounting for 30.9%, 27.6%, 17.5%, and 15.4% respectively [17].

In a study published in *hemodialysis international* by Chua et al. in 2003, the authors aimed for identification and resolution of DRPs in HD patients, after a thorough review of patients' clinical records and medications multiple DRPs were identified, and recommendations for resolution were presented to the nephrologist in charge; if the recommendations were accepted; monitoring was carried out for 2 weeks to assess the outcome of each intervention. during the duration of the study that lasted for 3 months, 31 patients completed the study, 83 DRPs were identified, and 73 interventions were made. The most common DRP was underdosing accounting for 35% of all identified DRPs, it was found that the interventions improved clinical outcomes in 54% of cases. The authors concluded that DRPs are highly prevalent in HD patients, but can be reduced through the integration of clinical pharmacy services in HD care[18].

In 2005, Manley et al. published a pooled analysis they conducted to assess the frequency, types, and severity of MRPs and extrapolate the data to the whole population of the US. Through their review of published studies between 1962 and March 2004, they pooled MRPs into 9 categories regarding indications, dosing, ADRs, laboratory monitoring, and problems with receiving medications. The authors identified 1,593 MRPs in 395 patients, the most frequent MRP was defective laboratory monitoring (23.5%), followed by indications without medication therapy (16.9%), subtherapeutic dosing (11.2%), and overdosing (9.2%). The study concluded that pharmacists should be fundamental members of the dialysis healthcare team; since pharmacists are trained to deal with MRPs. A reduction in MRPs can lead to a better quality of life (QoL) and decrease morbidity and mortality [19].

In a study by Ong et al., the pharmacist was able to identify 199 DRPs in 47 ESRD patients (27 HD patients, 14 PD patients, and 9 patients admitted for dialysis initiation) over 3 months. 92% of the patients suffered from at least one DRP on admission, on average, the number of DRPs per patient was 4.2 ± 2.2 . The most

common DRP was "indication without drug therapy" accounting for 51.3% of all identified DRPs. The study showed that 65% of the DRPs were associated with gaps in the transfer of medical information between healthcare professionals as well as healthcare providers and patients, revealing a need for an improvement in communication to prevent a large number of DRPs [20].

Another study conducted in New Zealand identified DRPs in 92% of the 64 HD patients participating in the study, with a total of 278 DRPs; the most common DRP was "lack of adherence to drug regimen" accounting for 33% of the identified DRPs, "a need for dose reduction" accounted for 9.3%, and "indication without drug therapy" accounted for 8.6% of total DRPs [21]. In a study evaluating a medication reconciliation program that is pharmacy-based, 376 discrepancies within medication records in addition to 64 MRPs were identified in 93 HD patients, the most common discrepancy was related to drug omission, while "indication without drug use" represented the most common MRP. The pharmacists recommended a total of 440 interventions of which 77% were accepted by the physician. The study shows that a pharmacy-based medication reconciliation and review program can affect HD care positively [22].

DRPs in developing countries:

In 2011, Castelino et al. published a study aiming to identify MRPs in patients with kidney disease, and also to point out the contribution of clinical pharmacists in resolving MRPs. The study was conducted in India, in Jagadguru Shri Shivaratheeshwara (JSS) Medical College Hospital renal unit. The study included patients undergoing dialysis in addition to patients referred to nephrologists by other specialists. The authors identified 327 MRPs in 308 patients over 9 months, the most common MRPs identified were overdose and ADRs, accounting for 19.3% and 19.0% respectively. Cardiovascular drugs and anti-infective agents were the most common medications associated with MRPs (33.6% and 26.3% respectively). The clinical pharmacists recommended modifications that caused a change of therapy in almost 85% of the cases. The authors concluded that the contribution of a clinical pharmacist can improve overall patient care [23].

A cross-sectional study conducted in the HD outpatient unit of king Abdelaziz medical city, Jeddah, Saudi Arabia aimed at evaluating the prevalence of polypharmacy as well as MRPs and assessing their predictors, the study found that polypharmacy was prevalent in 97.6% of the patients. Drug use without indication was the most predominant MRP (36%), followed by subtherapeutic dosing of medication (23%), and overdosing of medication (15%). The study concluded that polypharmacy is highly prevalent among Saudi HD patients, therefore, a review of medications conducted by pharmacists is needed to identify MRPs and optimize medication use [24].

In a cross-sectional multi-centered study that included three HD centers in Jordan to investigate treatment-related problems (TRPs) affecting Jordanian HD patients, the authors found the number of TRPs to be 1018 in a total of 160 participants, adverse events came on top of the list of TRPs accounting for 27%, followed by indication related errors and dosing errors (24% and 21% respectively). A positive correlation was found between the number of TRPs and age, the number of comorbidities, the number of medications taken by the patient, as well as the number of hospital admissions in the past year [25].

Authors	year	Aim of study	Number of patients	Results
(15)	1997	Evaluation of DRPs and impact of clinical pharmacy services.	-	126 DRPs were identified, 102 interventions were made.27.5% of identified DRPs were drug interactions.
(16)	2003	Assess MRPs type and appearance in HD patients.	-	33.5% of MRPs were dosing problems, 20.7% were ADRs, and 13.5% were indications without treatment.
(17)	2003	Assess factors associated with MRPs in HD patients.	133 patients	An average of 3.6 ± 1.8 MRPs was found per patient. The number of MRPs increases with the number of comorbidities. The most common MRP was drug use without indication (30.9%).
(18)	2003	Identification and resolution of DRPs in HD patients.	31 patients	83 DRPs were identified, 73 interventions were made. Underdosing was the most common DRP (35%).
(19)	2005	Analysis of published data on types, frequency, and severity of MRPs to extrapolate data to all US population.	395 patients	1,593 MRPs were identified. The most common MRP was inappropriate laboratory monitoring (23.5%).
(20)	2006	Assess DRPs in ESRD patients.	47 ESRD patients	A total of 199 DRPs were identified in 3 months, the most common was indication without drug therapy (51.3%).
(21)	2009	Evaluation of DRPs in HD patients.	64 HD patients	278 DRPs were identified, the most common was non- adherence to medications (33%).
(22)	2016	Evaluation of pharmacy-led medication reconciliation program.	93 HD patients	64 MRPs were identified; the most common was indication without drug use.

Table 1. summary o published studies on DRPs in HD patients in developed countries.

 Table 2.
 Summary of published studies on DRPs in HD patients in developing countries.

Published studies	year	Aim of study	Number of patients	Results
(23)	2011	Identify the nature and extent of MRPs in renally compromised patients.	308 patients	327 MRPs were identified in 9 months. Overdose and ADRs accounted for 19.3% and 19% respectively.
(24)	2018	Evaluate the prevalence of polypharmacy and MRPs.	-	97.6% of the patients suffered from polypharmacy. The most common MRP was medication use without indication (36%).
(25)	2021	Investigate DRPs affecting HD patients.	160 patients	1018 TRPs were identified, the most common were ADRs (27%). A Positive correlation was found between the number of TRPs and age, the number of comorbid conditions, and the number of medications.

DRPs in Egypt:

In 2021, Nagib et al. published a study evaluating the impact of clinical pharmacy services in an outpatient HD unit in Alexandria, Egypt, on the health outcomes of the patients. Clinical pharmacists collected all relevant data and reviewed the collected data for the Presence of DRPs. The identified DRPs were documented and resolved by the team of clinical pharmacists. Clinical pharmacists identified 685 DRPs during 19 months, the most common DRPs were improper drug dose and inappropriate drug selection (45.8% and 18.9% respectively). In

addition, the researchers also documented an increase in the proportion of patients achieving target levels of calcium, hemoglobin, and phosphorous after implementation of the clinical pharmacy program, showing that the inclusion of clinical pharmacy services not only led to the discovery and resolution of many DRPs; but also improved healthcare markers of the patients [26].

The implication of clinical pharmacy services in HD care:

In a study published by Tang et al., aiming to evaluate the effectiveness of clinical pharmacist interventions in the HD unit; a clinical pharmacist provided routine therapeutic interventions, 91.7% of the recorded intervention (205 interventions) were adopted by the medical team, most of the recommended therapeutic interventions were initiated as a response to abnormalities in the results of laboratory tests. The interventions were aimed at selection of drug, selection of dose, therapeutic monitoring, and discontinuation of drugs (32.2%, 24.4%, 24.4%, and 19% respectively). 90.5% of the accepted interventions resulted in positive patient outcomes [27].

In 1994, Kaplan et al. published a study that included 30 patients in an outpatient HD unit at a university hospital, the pharmacist provided 114 therapeutic recommendations of which 76% were accepted by the prescriber and 70% were carried out. The study showed that pharmacist significant the provided recommendations in this patient population [28].

In a study by Pai et al., 104 HD patients were randomly assigned to receive either pharmaceutical care provided by a clinical pharmacist, or standard care provided by a nurse, the study was conducted in a non-profitable university dialysis clinic for 2 years. By the end of the 2-year follow up, 530 DRPs were identified and resolved, pharmaceutical care showed superior results regarding drug use as it decreased by 14% compared with standard care (P < 0.05), pharmaceutical care also led to a significant decrease in all-cause hospitalization compared to standard care (mean \pm SD 1.8 \pm 2.4 vs 3.1 \pm 3 hospitalizations, p=0.02). the authors concluded that the implication of pharmaceutical care is associated with a major improvement in HD patients' outcomes [29].

In another study by Pai et al., the authors evaluated the effect of pharmaceutical care (PC) on the health-related quality of life (HRQOL) of HD patients. 61 patients were included in the pharmaceutical care (PC) group, while 46 patients were included in the standard of care (SOC) group by random selection (total number of patients=107). QoL was assessed using the renal quality of life profile (RQLP) which was given to patients at baseline, after 1 year, and after 2 years of baseline. The study showed that patients receiving PC didn't have worsened HRQOL after 1 year and were apple to sustain HRQOL for one additional year, compared to the (SOC) group who had significantly worse scores of ROLP after one year [30].

In a study published in 2017 by Chia et al., pharmacists identified 515 DRPs and resolved 429 of the identified DRPs in Singaporean HD patients, proving that a collaborative care (CC) program with pharmacist contribution is superior to the usual care (UC) program without the pharmacist contribution in reducing DRP occurrence. The CC model also reduced unplanned hospital admissions by 27% and shortened the length of stay (LOS) by 1.3 days [31].

A study by Chen et al. showed that the participation of a clinical pharmacist in the nephrology ward caused a reduction in ADRs and proved to have a cost-saving effect. The study compared the number of pharmacist interventions one year before and after the employment of a clinical pharmacist in the nephrology ward. Pharmacist interventions represented a total of 824 preintervention compared to 1977 post-intervention, the estimated saved cost was NT\$52,072 pre-intervention compared to NT\$144,138 post-intervention, while the estimated saved costs of preventable ADRs were NT\$3,383,700 and NT\$7,342,200 pre-intervention and post-intervention respectively [32].

Another study showed that patient counseling provided by a clinical pharmacist was effective in improving HRQOL and awareness in HD patients. The study included 84 patients, half of the study subjects were assigned to the control group and the other half to the case group receiving pharmaceutical care, a survey administered before and after one month of counseling showed a major improvement in the case group compared to the control group [33].

In a study by Daifi et al., a clinical pharmacist conducted medication reviews with HD patients to assess the prevalence of MRPs, the clinical pharmacist detected 1,403 MRPS with 9 problems per patient on average. The most common MRPs were related to adherence (31%), while the most common medication classes associated with MRPs were anti-hypertensives (37%), vitamin D analogs, and calcimimetics (29%). The contribution of the clinical pharmacist saved a projected total of US \$447,355. The authors concluded that pharmacist contributions in HD facilities have a positive impact on medication management and cost savings [34].

Recommendations

The knowledge acquired from the mentioned studies should inspire necessary changes to decrease the prevalence of DRPs in this susceptible patient population, the following are the major recommendations:

1. the administration of every medical center must adopt a standard treatment protocol based on updated trustworthy guidelines and ensure its application by all healthcare workers.

2. incorporating clinical pharmacy services responsible for reviewing patients' treatment and tailoring the best management plan for each specific patient.

3. using a computerized system of medication review to detect drug-drug interactions before dispensing the medications to the patients.

4. starting a patient-education program informing the patients about their treatment and the expected side effects and how to deal with them.

Conclusion

Hemodialysis represents the main modality of RRT in Egypt. HD patients are a vulnerable population due to multiple comorbidities and numerous consumed medications exposing them to DRPs. An increasing global interest in the identification and resolution of DRPs to improve patient outcomes and decrease morbidity and mortality led to a leap in studies regarding DRPs definitions, classifications, types, and frequency. Clinical pharmacy services in the HD unit have proven their worth in decreasing the appearance of DRPs, many modifications can be made in healthcare systems to provide better health services and improve patient outcomes. As noticed from the timeline of the studies in the literature, few studies tackled the subject of DRPs in developing countries with only one study including the Egyptian population, revealing a need for more research regarding DRPs in the Egyptian HD population.

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