

Evaluation of Compliance to Treatment Guidelines and Goals of Therapy among Palestinian Hemodialysis Patients

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ABSTRACT

Patients on hemodialysis usually need management of diabetes, hypertension, dyslipidemia, anemia, and bone mineral disorder. This study was conducted to assess prescribing pattern, to evaluate compliance to treatment guidelines and goals of therapy in hemodialysis patients. This study was an observational retrospective cohort study; it was conducted at Hebron governmental hospital / Palestine. All adult patients on chronic hemodialysis were included. All information were collected from governmental electronic health record (AviCenna HIS program), and patients were asked to answer some questions. During the study period 158 patients were prescribed 1567 medication orders with a mean of 9.92 ± 2.94 . The majority of the patients (72.2%) had Hypertension. The target predialysis blood pressure was achieved in 77.2% of the patients (70.5% of the males vs 87.3% of the females; P-value = 0.014), and post dialysis blood pressure was achieved in 57.6% cases. Diabetes was a comorbid disease in 36.7% patients and hemoglobin A1c (HbA1c) test was not performed for these patients. Patients with total cholesterol levels of < 200 mg/dl were 78.3% patients. Regarding triglycerides levels, 96.2% had levels of < 500 mg/dl. In the management of anemia, patients who reached goal hemoglobin (Hb) of 11-12 mg/dl according to the national kidney foundation (NKF) guidelines were 8.9% patients only. If kidney disease improving global outcome (KDIGO) guidelines are used (Hb 9-11.5 mg/dl) the patients in this range were 43.0% cases. Transferrin levels were not measured. Iron was used by 69.9% of the patients, and erythropoietin stimulating agents (ESA) by 5.1% of the patients as it was not available in the hospital. No data was available for calcium, and parathyroid hormone levels. Target phosphorus level was obtained in 12.0% of the patients according to the NKF guidelines. If serum phosphorus normal range of 2.5–4.5 mg/dl is used according to KDIGO guidelines, this target was achieved in 4.4% patients only. The results reflect a poor compliance to treatment guidelines. The target levels for treatment are not achieved in many HD patients. The medications are not prescribed optimally to the patients and many investigations and laboratory tests are not performed.

Keywords: Compliance, Guidelines, Hemodialysis, Kidney, Palestine

INTRODUCTION

Chronic kidney disease (CKD) is a growing epidemic worldwide (1). It is associated with poor prognosis, development of premature cardiovascular disease and increased mortality (2). Treatment of CKD aims to slow progression to end-stage renal disease (ESRD) and to prepare for it. Therapy is usually started

at an asymptomatic condition detected only by laboratory testing (3). The popu-

lation with ESRD is expanding at a rate of around 7% per year worldwide (4). The increase in ESRD incidence could be due to the increase of patients with CKD and the rate of their disease progression, decreases in competing mortality, and/or increasing treatment availability (5). The leading cause of ESRD is diabetes followed by renal vascular disease, including hypertension (6). The

maintenance therapy for ESRD is by renal replacement therapy, through dialysis or kidney transplant. Clinical management of dialysis patients often involves treatment of multiple comorbid conditions, in which dialysis patients are prescribed on average 9-10 oral medications and 2-3 parenteral medications (7, 8). Patients on hemodialysis (HD) need to use a large number of medications to control their disease complications and other comorbid diseases. In Palestine, limited information about this population is available. To the best of our knowledge, prescribing pattern and adherence to treatment guidelines in HD patients were not studied before in our country, therefore, it would be important to evaluate current situation and compare it with international guidelines for treatment to improve the quality of care provided to HD patients. Findings can help in developing educational programs and interventions to improve compliance with international treatment guidelines in HD patients.

The aims of this study were to assess prescribing pattern and to evaluate compliance to treatment guidelines of National Kidney Foundation (NKF) and Kidney Disease: Improving Global Outcomes (KDIGO) for anemia, bone disease, diabetes mellitus, hypertension and dyslipidemia in hemodialysis patients in Hebron governmental hospital and to evaluate if the outcomes of treatment (e.g target hemoglobin, calcium, phosphorus, HB A1c, blood pressure (BP), etc) meet the recommended goals.

MATERIALS AND METHODS

The study was an observational retrospective cohort study. It was carried out at Hebron governmental hospital /Palestine between the first of March 2014 and the end of April 2014. Palestinian Ministry of Health (MOH) is the main health care provider for the ESRD management in Palestine, where treatments of ESRD are given free to the patients. According to the Palestinian Ministry of health report in 2013 there are 800 patients on HD in the West Bank hospitals with 141

dialysis machines distributed among 10 hemodialysis units (8).

All adult HD patients (158 patients) who had their HD sessions in that hospital during the study period and met the inclusion criteria were asked to participate in the study. Exclusion criteria included patients who were younger than 18 years of age or patients who required HD for acute renal failure or were on HD for less than one month.

Data collection form was prepared after literature review of guidelines and previous studies. All information were collected from the governmental electronic health records (AviCenna HIS program), which was used to identify chronic HD patients. Verbal consent was obtained from the patients. All of them accepted to be involved in the study. The file for every patient was reviewed; baseline demographics, comorbid conditions, vital signs, laboratory data, and information about the medications were collected. Regarding the medications, the last medication order was reported and for the laboratory tests the last reading in the file was documented. Also, patients were asked to answer some questions about sociodemographic factors and other medications purchased or used by them when data were not found in (AviCenna HIS program).

The study protocol was authorized by the Institutional Review Boards (IRB) of An Najah National University and the Ministry of Health before initiation of this study.

As we do not have our own national guidelines for treatment of ESRD patients, guidelines by the National Kidney Foundation Kidney Disease/Dialysis Outcomes Quality Initiative (NKF-KDOQI) and Kidney Disease: Improving Global Outcomes (KDIGO) were used to compare the practice (medications and target goals) in this study with these guidelines (Table 1). These guidelines are very well-known and are being followed in many countries. Treatments of diabetes, hypertension, dyslipidemia, anemia and bone disease were included.

Table (1): Summary of KDOQI and KDIGO clinical practice guidelines.

Recommended medications	Goals	Reference
Diabetes		
Insulin regimens Oral hypoglycemic agents should be used with caution (e.g. glyburide, glipizide, and glimepride) Metformin is contraindicated	HbA1c of around 7.0%	NKF, 2007 NKF, 2012
Hypertension		
ACE inhibitors or ARBs should be preferred	Predialysis BP <140/90mmHg Postdialysis BP <130/80mmHg	NKF, 2005
Dyslipidemia		
Statins are preferred Statins or statin/ezetimibe combination not to be initiated after HD if they were not used before	LDL cholesterol < 100 mg/dL Triglycerides < 500 mg/d	NKF, 2005 KDIGO, 2012
Anemia		
Erythropoietin stimulating (ESA) agent and iron	Hb level 11-12 g/dl Serum ferritin level > 200 ng/mL Transferin > 20% Hb level 9-11.5 g/dl Serum ferritin level > 500 ng/mL Transferin > 30%	NKF, 2007 NKF, 2006 KDIGO, 2012
Bone metabolism and disease		
Calcium-based phosphate binders and non calcium-, containing phosphate-binding agents (such as sevelamer HCl) Active vitamin D	Phosphorus 3.5 - 5.5 mg/dL Corrected total calcium 8.4 - 9.5 mg/dL PTH 150 - 300 pg/mL. Serum phosphorus and calcium in the normal range iPTH levels in the range of approximately 2-9 times the upper normal limit for the assay	NKF, 2003 KDIGO, 2009

Statistical analysis was performed by using Statistical Package for Social Sciences (SPSS version 16.0) program. Descriptive statistics were carried out for all variables. Mean \pm standard deviation was computed for continuous data. Frequencies (percentages) were calculated for categorical variables. Categorical variables were compared using Chi-square. When categorical and continuous variables were compared; independent student T test or Mann-Whitney test according to the normality were used. Association between continuous variables

was assessed with Pearsons' or Spearman's test according to the normality. A p-value of less than 0.05 was considered to be statistically significant for all analyses.

Socio-demographic characteristics of patients included in the study

The number of HD patients was 158 patients; 95 males (60.1%) and 63 females (39.9%). Age was between 18-92 years, the mean age was 49.6 \pm 18.0 years. The mean weights before and after dialysis were 72.87 \pm 20.0 kg and

70.60±19.5 kg respectively, and the mean height was 166±8.9 cm.

All the patients were from Hebron region, 75 (47.5%) of them were from the city, 82 (51.9%) were from the villages, and only one patient was (0.6%) from a camp.

The highest percentage of participants had a middle school degree (39.2%). Most of HD patients (90.5%) were not working and (17.7%) were still smoking. Socio-demographic characteristics of the patients are presented in (Table 2).

Table (2): Socio-demographic characteristics of the 158 patients.

Characteristics	Mean	
Age	49±18 years	
Weight before dialysis	72.87±20 Kg	
Weight after dialysis	70.60±19.5 Kg	
Height	166±8.9 cm	
Characteristics	Frequency	Percentage
Patients' gender		
Male	95	60.1%
Female	63	39.9%
Living place		
City	75	47.5%
Village	82	51.9%
Camp	1	0.6%
Educational level		
Primary and illiterate	36	22.8%
Middle school	62	39.2%
High school	31	19.6%
University graduate	26	15.6%
Postgraduate	3	1.9%
Working		
Yes	15	9.5%
No	143	90.5%
Smoking		
Smoker	28	17.7%
Not smoker	130	82.3%

RESULTS

Prescribing pattern for HD patients

During the study period 158 HD patients were prescribed 1567 medication orders of 103 different medications, 49 medications for the management of chronic illness, and 54 medications for acute illness. The patients were taking a minimum of 2 and a maximum of 18 medications, with a mean of 9.92±2.94 (Figure 1).

The most commonly prescribed medications were calcium carbonate (91.8%), followed by alfacalcidol (84.8%), then iron/folic acid (69.6 %). The top twenty used medications are presented in (Table 3).

Table (3): The top twenty used medications among HD patients (n= 158).

NO	Medication	Frequency	Percentage (%)
1	Calcium Carbonate	145	91.8%
2	Alfacalcidol	134	84.8%
3	Iron/ folic acid	110	69.6%
4	Amlodipine	105	66.5%
5	Paracetamol	76	48.1%
6	Aspirin	70	44.3%
7	Folic Acid	67	42.4%
8	Atorvastatin	63	39.9%
9	Ranitidine	61	38.6%
10	Insulin Mixtard	54	34.2%
11	Omeprazole	50	31.6%
12	Furosemide	43	27.2%
13	Diclofenac Sodium	37	23.4%
14	Allopurinol	32	20.3%
15	Ceftriaxone	32	20.3%
16	Atenolol	27	17.1%
17	Amoxicillin/Clavulanic Acid	25	15.8%
18	Sevelamir	25	15.8%
19	Chlorpheniramine	24	15.2%
20	Isosorbide-5-Mononitrate	22	13.9%

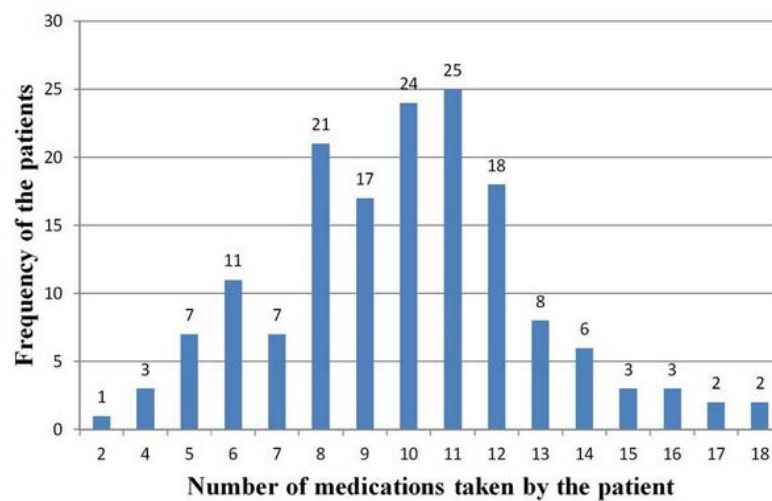


Figure (1): Number of medications used by the patients.

Dialysis data

In this study there was one patient who spent 21 years on HD. One month was the minimum duration, and 252 months was the maximum. The length of each dialysis session was 180 minute in most patients 152 (96.2%), other options were 210, or 240 minutes, and the number of dialysis session per week were 1, 2, 3, and 4. Most of the patients had 3 sessions.

In HD patients, potassium level was measured for only 68 patients with a mean of 5.08 ± 0.97 mg/dl and a range of (2.4-7.1 mg/dl). Blood urea nitrogen (BUN) and serum creatinine were measured for all patients and the mean was 67.65 ± 24.31 mg/dl (range 7.8-169 mg/dl) and 7.7 ± 2.68 mg/dl (1.3-14.8 mg/dl) respectively.

Compliance to treatment guidelines for diabetes

Fifty eight (36.7%) patients were found to have diabetes. Insulin mixtard was used by 54 of the patients, four were taking glibenclamide, three were taking insulin actrapid and two of them were on oral metformin. HgA1c was not performed in the hospital, and data about it was missing and there was no follow up for it.

Fasting blood sugar levels was tested for all HD patients who had or had not diabetes and random was tested for 41 patients, only 21 of them were diabetic. Among the 58 patients with diabetes, 25 (43.1%) patients had fasting blood sugar test < 130 mg/dl, while random blood sugar test was performed for 21 diabetic patients, and 9 (42.8%) of them had their readings below 180 mg/dl. No statistically significant association between diabetes control and any other related variable was found.

Compliance to treatment guidelines for hypertension

Among patients, 114 (72.2%) had hypertension. Many drugs were used to control their blood pressure such as enalapril, losartan, valsartan, amlodipine, nifedipine, diltiazm, atenolol, bisoprolol, carvedilol, propranolol, methyldopa, doxazocin, hydrochlorothiazide, and furosemide. Amlodipine was the most commonly antihypertensive medication used by 105 (66.5%) of the patients.

The target predialysis blood pressure of less than 140/90 mmHg was achieved in 122 (77.2%) patients (70.5% of the males vs 87.3% of the females; P-value = 0.014). On the other hand, postdialysis blood pressure of less than 130/80 mmHg was achieved in 91 (57.6%) patients only. There was no statistically significant association between

postdialysis blood pressure and socio-demographic and clinical variables. Predialysis blood pressure correlated with postdialysis blood pressure ($r = 0.236$, p value = 0.003) based on Pearson's test.

Compliance to treatment guidelines for dyslipidemia

Among the 158 patients, atorvastatin was used by 63 (39.9%), and rosuvastatin, bezafibrate were used in one patient only. Total cholesterol and triglyceride were tested for the patients. The mean total cholesterol was 164 ± 50.24 mg/dl ranging from 65 to 364 mg/dl. Patients with total cholesterol levels of less than 200 mg/dl were 123 (78.3%) patients from 157 for whom total cholesterol was measured. Regarding triglycerides levels, they ranged from 43 to 622 mg/dl. The majority of the patients 96.2% had triglycerides levels of <500 mg/dl. There was an association between the control of total cholesterol and triglycerides (Chi-square, p value = 0.006).

Compliance to treatment guidelines for anemia

Iron was used by 110 (69.9%) patients, and erythropoietin by 8 (5.1%) patients only. Mean hemoglobin level was 8.84 ± 1.52 mg/dl with a range (5.8-14.4 mg/dl), Patients who reached goal Hb of 11-12 mg/dl according to the NKF guidelines were 14 (8.9%) patients only. If KDIGO guidelines are used, these guidelines accept a Hb level between 9-11.5 mg/dl but not to exceed 13 mg/dl, the patients in this range reach 68 (43.0%) cases.

Target ferritin level of > 200 ng/ml according to NKF guidelines was achieved in 91 (57.6%) patients. Target ferritin level of > 500 ng/ml according to KDIGO guidelines was achieved in 74 (46.8%) cases. There were no data available about ferritin level for 51 (32.3%) patients. Transferin test was not performed for all the patients.

No statistically significant association between anemia control and socio-

demographic or clinical factors was found.

Compliance to treatment guidelines for bone mineral disorder

There was no data available for calcium, or PTH levels in HD patients. Only phosphorus level was measured but not for all the patients. Calcium carbonate was used by 145 (91.8%) patients, sevelamir by 25 (15.8%) patients, and alfacalcidol by 134 (84.8%) patients. Phosphorus target level of 3.5-5.5 mg/dl according to the NKF guidelines was achieved in only 19 (12.0%) patients, 128 (81.0%) had phosphorus levels out of the target, and 11 (7.0%) of the patients had no data. If serum phosphorus normal range of 2.5-4.5 mg/dl is used according to KDIGO guidelines, this target was achieved in 7 (4.4%) patients only.

DISCUSSION

In this study, the 158 HD patients were prescribed 1567 medications of 103 different drugs with a mean of 9.92 ± 2.94 . The number of medications in this study is close to other studies that included CKD and ESRD patients where the mean was around 9 medications (9, 10). However, this is lower than a study from the USA where the mean of medications prescribed for HD patient reached 12.3 ± 0.5 medications (11), this may be due to not following the same guidelines or the unavailability of some medications in our hospitals. On the other hand, it was higher than a Japanese study where the mean was 7.2 medications (12). Polypharmacy is common and expected among HD patients, this increases the possibility of drug-related problems, and the need for extra counseling and monitoring.

The most commonly prescribed medications for HD patients in this study were calcium carbonate (91.8%), followed by alfacalcidol (84.8%), then iron/folic acid (69.6 %). This is expected based on the complications of the disease. A study conducted at a nephrology unit in a Malaysian hospital showed that calcium carbonate was the most com-

monly prescribed medication also, followed by a combination of folic acid and vitamin B complex, and the third commonly prescribed medication was metoprolol (9). In a study from India, the five most commonly prescribed drugs were multivitamins, iron, folic acid, calcium carbonate, and calcitriol (10).

In this study, 58 (36.7%) patients had diabetes, among them, 54 were on mixtard insulin, 4 were on glibenclamide, 3 were on actrapid insulin and 2 were on metformin. According to the NKF guidelines insulin and glibenclamide are accepted choices to be used. First generation sulfonylureas (e.g., chlorpropamide, tolazamide, and tolbutamide) should be avoided in patients with CKD because they have increased half-lives and the risk of hypoglycemia. Glipizide is the preferred second-generation sulfonylureas as it does not have active metabolites and does not increase the risk of hypoglycemia in patients with CKD (13). Regarding metformin is cleared by the kidneys, so its use in CKD is restricted. Black-box warning was mandated by the FDA regarding the risk of lactic acidosis. The label indicates that metformin should not be used in men with a SCr of 1.5 mg/dL or in women with a SCr of 1.4 mg/dL (13), two patients in this study were prescribed this medication.

The guidelines evaluate diabetes control according to Hb A1c test. In this study no HbA1c values were available in the files and these tests were not performed for diabetic hemodialysis patients. Fasting and random blood glucose levels were the only available tests. Fasting blood glucose test was done for all HD patients once every month, it is recommended to test blood glucose frequently for diabetic patients. However, measuring glucose levels in patients without diabetes with this frequency might not be needed. Among the 58 patients with diabetes, 25 (43.1%) patients had fasting blood sugar test < 130mg/dl, while random blood sugar test was performed for 21 diabetic patients, and 9

(42.8%) of them had their readings below 180mg/dl. The American Diabetes Association recommends preprandial plasma glucose of < 130 mg/dl and postprandial levels of < 180 mg/dl for diabetic patients in general (14). It can be noticed here that more than half of diabetic patients did not achieve these levels. Treatment of diabetes in HD patients needs to be improved, monitoring of Hb A1c is needed to guide treatment.

Among patients, 114 (72.2%) of HD patients had hypertension, this is expected and similar to other parts of the world where 60% to 90% of maintenance HD patients have hypertension. Hypertension in these patients often is poorly controlled despite the use of multiple medications (15, 16).

Amlodipine was the most commonly antihypertensive medication used by 105 (66.5%) of the patients, 11 (7%) were on enalapril, 5 (3.2%) were on losartan, and 3 (1.9%) were on valsartan. This low use of ACE inhibitors and ARBs is not in agreement with the NKF recommendations in which drugs that inhibit the renin angiotensin system are preferred for the management of hypertension in HD patients to decrease cardiovascular risk (17). In a review by Enam et al in 2014, they consider beta-Blockers, CCBs, ACE inhibitors, and ARBs as appropriate primary choices for HD patients (18).

The target predialysis blood pressure of < 140/90 mmHg was achieved in 123 (77.8%) patients, while postdialysis blood pressure of < 130/80 mmHg was achieved in 91 (57.6%) patients only. This is better than recent results from our country where 33 (51.6%) patients attained predialysis blood pressure goals and 31 (48.4%) reached the postdialysis goal (19). However, there is a room for improvement. To control blood pressure, not only medications are important, restrictions in sodium and fluids are recommended. Postdialysis blood pressure correlated with predialysis values, so if it is possible to control BP between ses-

sions, the control will improve after dialysis also.

According to the NKF, LDL cholesterol levels should be below 100 mg/dL, and statin can be used to achieve this target. In this study LDL levels were not tested, instead, total cholesterol and triglycerides were measured; atorvastatin was used by (39.9%). Patients with total cholesterol levels of < 200 mg/dl were 123 (78.3%). The majority of the patients 151 out of 157 (96.2%) had triglycerides levels of <500 mg/dl. Dyslipidemia may increase risk of ischemic stroke and cardiovascular mortality. The control of dyslipidemia in this study is better than other conditions and complications as most of the patients had accepted levels of total cholesterol and triglycerides, however, it is recommended to test LDL cholesterol and concentrate on dietary counseling.

In this study complete blood count was done periodically once a month, and (91.1%) of the HD patients had anemia defined as Hb levels < 11mg/dl according to the NKF guidelines (20) and even if KDIGO guidelines are used (21), these guidelines accept a Hb level between 9-11.5 mg/dl but not to exceed 13 mg/dl, the patients in this range were 68 (43.0%) cases which means that many patients in the study are anemic. Renal data from the Arab World, showed that control of anemia, was not satisfactory as 50% of study patients had Hb levels < 10 g/dl in 103 HD patients in Libya (22).

According to NKF (20) the ESAs are critical components in managing the anemia of CKD, where IV administration is preferred, and effective use of iron agents, guided by appropriate testing of iron status is recommended. Iron was used in (69.9%) of the patients, but erythropoietin IV route was used by 8 (5.1%) out of 158 patients only, as it was not available during study period in the hospital due to financial problems in the MOH, this medication is expensive to be purchased by the patients. Target ferritin level of > 200 ng/ml according to NKF guidelines was achieved in 91 (57.6%)

patients. Target ferritin level of > 500 ng/ml according to KDIGO guidelines (21) was achieved in 74 (46.8%) cases. There were no data available about ferritin level for 51 (32.3%) patients. Transferin test was not performed for all the patients. It is clear that better treatment for anemia is recommended and more investigations are needed.

According to NKF Serum levels of calcium, phosphorus, and PTH should be measured in all patients with CKD and GFR<60 mL/min/1.73m². A study in Libya in 2006 found that the target serum level of intact parathyroid hormone (PTH) was reached in 17.4% of the patients, and only 30% of the patients achieved target serum calcium (8.4-9.5 mg/dl) (22). But in this study calcium and parathyroid hormone serum level were not measured for the patients, because they are not available in the hospital's laboratory, and are expensive to be done out in private laboratories. During this study period only one patient did these tests on his own account. Almost all the patients (91.8%) were taking calcium carbonate, in addition to (84.8%) were taking alfacalcidol to reduce the serum levels of PTH to a target range of 150 to 300 pg/mL as recommended by NKF (23). Target phosphorus level of (3.5-5.5 mg/dl) was reached in (12%) of the HD patients, and according to KDIGO guidelines (24), this target was achieved in 7 (4.4%) patient. Only 25% of the HD patients were taking phosphate binder sevelamir. Management of chronic kidney disease mineral and bone disorder requires interdisciplinary team interventions that include dietary modification, medications, and adequate dialysis therapy. Optimizing adherence to diet and medications requires an educated and motivated patient, and patient support system (25).

In summary, compliance to treatment guidelines was low; to achieve a good compliance to treatment guidelines in HD patients, cooperation between patients, doctors, dietitians and clinical pharmacists is needed. In each HD de-

partment a nephrologist, and a clinical pharmacist should be available to follow up the patients. All the laboratory test, and medications to control diabetes, hypertension, dyslipidemia, anemia (especially ESA), and bone mineral disorder should be available, which is the responsibility of the ministry of health. Following international guidelines in treatment to reach the recommended goals in the previous diseases and complications can improve quality of life of patients and decrease morbidity and mortality (15, 21).

The first limitation of this study is that it was performed in dialysis center in Hebron Governmental Hospital so it might not be representative to the practice in other dialysis centers in other hospitals. Another limitation is the unavailability of many medications, and laboratory tests which are important to measure compliance to treatment guidelines. The last limitation was the unavailability of national guidelines to compare with and the presence of different international guidelines.

CONCLUSIONS

This study shows a poor level of compliance to treatment guidelines according to NKF and KDIGO guidelines for diabetes, hypertension, dyslipidemia, anemia, and bone mineral disorder, where target levels for treatment are not achieved in many HD patients. The medications are not prescribed optimally to the patients and many required investigations and laboratory tests are not performed.

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CONFLICT OF INTERESTS

The authors declare that they have no competing interests.

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