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Original Article

The Compatibility of the Treatment Modalities to the Recommendations of the Kidney Disease Outcomes Quality Initiative Guideline in Chronic Kidney Disease Patients with Diabetes

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Abstract

Background: Diabetes mellitus (DM) and chronic kidney disease (CKD) are global growing health problems. Since DM is the major cause for CKD etiology, its development can be prevented with simple measures, like achievements of glycemic, lipid and blood pressure targets. This study aimed to evaluate whether the treatment goals for CKD patients with DM are achieved under the Kidney Disease Outcomes Quality Initiative (KDOQI) guideline.

Methods: Overall, 160 CKD patients with DM were enrolled in the study performed in Usak, Turkey from Jan 2016 to Jan 2018. Compatibility with treatment goals defined in KDOQI 2012 guideline for HbA1c levels, hypertension and dyslipidemia were evaluated retrospectively.

Results: Of 160 CKD patients [15 (9.4%) in stage 3a, 53 (33.1%) stage 3b, 51 (31.9%) stage 4 and 41 (25.6%) stage 5], 23 patients in stage 5 were on hemodialysis. Total compliance rate to hyperglycemia treatment was 94 of 160 patients (58.8%). Compatibility rates between different stages of CKD were similar. Hypertension was detected only in 134 patients. Sixty-six (49.3%) patients were compatible with the treatment goals, and as the CKD stages progressed, the rate of patients achieving hypertension treatment goals was declined (P=0.001). One-hundred and thirty-seven patients were not on hemodialysis and fifty-four (39.9%) of 137 patients achieved dyslipidemia goal. There was no difference between different stages of CKD.

Conclusion: Under KDOQI 2012 guideline, treatment goal for hyperglycemia was better achieved than the treatment goals for hypertension and dyslipidemia. In CKD patients with DM the physicians should be also focused on the treatment of hypertension and dyslipidemia.

Keywords: Chronic kidney disease; Diabetes mellitus; Treatment compliance

Introduction

The prevalence of diabetes mellitus (DM) is increasing worldwide. According to The International Diabetes Federation (IDF) 2017 report, 425 million people live with DM in the worldwide, and it is estimated to rise over 620 million by the year 2045 (1). In Turkey, the prevalence of

DM was reported as 13.7% (2); unfortunately, it is one of the countries where DM prevalence is increasing rapidly and seriously. Diabetes is also the major factor for the development of chronic kidney disease (CKD), another growing important health challenge. The prevalence of CKD is globally estimated as 13.4% (3). It is reported that 42.3% of patients with type 2 DM have CKD in the United States of America (USA) (4), and 44% of the early-stage patients with end-stage renal disease (ESRD) have DM (5). In Turkey, CKD prevalence is reported as high as 15.7% in general population, and this rate is anticipated to increase up to 32.4% in patients with DM in the following years (6).

The appropriate and successful treatment of DM and comorbidities such as hypertension and dyslipidemia are effective in the prevention of CKD development and progression, and to decrease the risk of cardiovascular diseases (7,8). The appropriate drug choices and dose adjustments for the treatment of hyperglycemia, dyslipidemia, and hypertension in patients with CKD is important, especially in those with stages 3-5 CKD (9,10).

The last Kidney Disease Outcomes Quality Initiative (KDOQI) guideline was published in 2012 to prevent the progression of kidney disease and reduce the cardiovascular risk in CKD patients with DM (5). The KDOQI guideline recommends the level of HbA1c as approximately 7% to control hyperglycemia, and for patients with hypertension, the levels of blood pressure (BP) should be equal to or under 130/80 mmHg for patients with albumin to creatinine ratio (ACR) ≥30 mg/g which defines albuminuria in a morning spot urine sample. For normoalbuminuric patients, however, BP levels should be under or equal to 140/90 mmHg in CKD patients with DM. In normotensive patients, it is reported that when microalbuminuria, an independent risk factor leading to disease progression is present, the guideline also recommends the treatments of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARB). Patients with DM and CKD that are not on dialysis should take statin or statin/ezetimib combination to decrease the cardiovascular risk (5, 11). The targets of lipid lowering therapy are specified in the previous guideline (12) that low-density lipoprotein cholesterol (LDL-C) should be <100 mg/dL in those with DM and CKD stages 1-4.

In this retrospective study, we aimed to evaluate the compatibility of the treatment goals in stage 3-5 CKD patients with DM to the following criteria of the 2012 KDOQI guideline: firstly, HbA1c level should be approximately 7% for the hyperglycemia control; secondly, for patients with hypertension BP levels should be 130/80 mmHg or lower for those with ACR ≥30 mg/g ~~albuminuria~~ and under or equal to 140/90 mmHg for normoalbuminuric patients; lastly, CKD patients with DM which are not on dialysis should receive the combination of statin or statin/ezetimib.

Materials and Methods

This retrospective study was conducted in the Nephrology Division and Dialysis Units of the School of Medicine of Usak University.

The study protocol was approved by the local Ethics Committee of the School of Medicine of Usak University. From January 2016 to January 2018, a computer database was searched, and 190 stage 3-5 CKD patients with DM were followed in the nephrology department for at least 3 months and detected within this period. One-hundred and sixty patients were found to be eligible for the analysis and enrolled into the study. The data of the patients about age, gender, creatinine, estimated glomerular filtration rate (eGFR) were calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, and HbA1c levels, blood pressure level, treatment of diabetes (diet, insulin, oral antidiabetics), and anti-hypertensive treatment from the patients' computer-based medical records were recorded on the patients' study chart. Based on eGFR, the stages of CKD were defined as stage 3a, moderate CKD (eGFR= 45-59 mL/min); stage 3b, moderate CKD (eGFR= 30-44 mL/min); stage 4, severe CKD (eGFR= 15-29 mL/min); stage 5, end-stage CKD (eGFR <15

mL/min). We investigated the differences between the different stages of CKD according to the compliance with the KDOQI guideline for the treatments of diabetes and CKD updated in 2012.

The data were analyzed with the Statistical Package for Social Sciences, version 22.0 for Windows (IBM, SPSS, Chicago, IL, USA). The descriptive statistics were applied to define the main characteristics of the patients. The Shapiro-Wilk and Kolmogorov-Smirnoff statistical tests were used to check the normality of the data. For comparisons of categorical variables and groups parametric and non-parametric tests were used. A *P* value less than 0.05 was defined as significant.

Results

One-hundred and sixty (95 males and 65 females) stage 3-5 CKD patients with DM were analyzed. The baseline characteristics of the patients are shown in Table 1. The mean age of the patients was 67.6±10.6 years, and the mean HbA1c level was 7.6±1.6. Of 160 patients, 15 (9.4%) had stage 3a CKD, 53 (33.1%) stage 3b, 51 (31.9%) stage 4 and 41 (25.6%) stage 5. Among stage 5 CKD patients, 23 were on hemodialysis (Table 1). Although stage 3b and 4 CKD patients had slightly higher mean HbA1c levels than those in stages 3a and 5 CKD patients, this difference did not reach a significant level (Table 2).

Table 1: Baseline characteristics of patients

Gender (male/female) (n) (%)	***95/65 (59.4/40.6)***
Age (yr)	67.6±10.6
BMI (kg/m^2)	29.3±5.4
Systolic blood pressure (mmHg)	133±22
Diastolic blood pressure (mmHg)	74±11
Duration of CKD (months)	74.9±20.3
Duration of DM (years)	14.3±8.4
Creatinine (mg/dL)	2.98±2
LDL cholesterol (mg/dL)	105.4±35.6
HbA1c (%)	7.6±1.6
eGFR (CKD-EPI) (ml/min/1.73 m^2)	25.5 (4-56)
Patients with stage 3a CKD n (%)	15 (9.4)
Patients with stage 3b CKD n (%)	53 (33.1)
Patients with stage 4 CKD n (%)	51 (31.9)
Patients with stage 5 CKD n (%)	41 (25.6)

BMI: Body mass index, CKD: Chronic kidney disease, CKD-EPI: Chronic kidney disease epidemiology collaboration equation, DM: Diabetes mellitus, eGFR: Estimated glomerular filtration rate, HbA1c: Hemoglobin A1c, LDL: Low density lipoprotein, n: number

Table 2: Mean HbA1c of patients with 3-5 stages of chronic kidney disease

Variable	***HbA1c (%)***
Stage 3a CKD patients	7.32
Stage 3b CKD patients	7.47
Stage 4 CKD patients	8.06
Stage 5 CKD patients	7.31

CKD: Chronic kidney disease, HbA1c: Hemoglobin A1c

The number of patients compatible with the hyperglycemia treatment goals recommended in the KDOQI guideline was found to be 94 (58.8%) out of 160 patients. In group comparisons, no difference was detected with respect to disease stages (Table 3). Hypertension was detected in

134 patients (83.8%) out of 160 patients. Sixty-two patients (49.3%) with hypertension were compliant to hypertension treatment goal considered to be ≤130/80 mmHg for patients with ≥30 mg/g albuminuria and ≤140/90 mmHg for normoalbuminuric patients, and none of the normotensive patients with ACR ≥30 mg/g received ARB or ACE inhibitors. In group comparisons, as the CKD stages increased, the rate and number of patients who achieved hypertension treatment goals declined significantly (*P*=0.001) (Table 3). Only 54 of 137 CKD patients not on hemodialysis were on statin treatment, and compliance rate to the lipid lowering treatment goal was 39.9% (Table 3). No statistically significant difference was found between the different CKD stages according to compliance to dyslipidemia goal. The great majority of patients (66.8%) were on insulin treatment (Table 4).

Table 3: Compliance of patients with different stages of CKD to the KDOQI guideline

	Hba1c levels should be ~7% Compliant/not Compliant (n, %) *	***Dyslipidemia treatment Compliant/not Compliant (n, %) *****	***Blood pressure treatment Compliant/not Compliant (n, %) ******
Stage 3a CKD patients	10/5 (66.7/33.3)	7/8 (46.7/53.3)	12/3 (80/20)
Stage 3b CKD patients	31/22 (58.5/41.5)	22/31 (41.5/58.5)	29/21 (58/42)
Stage 4 CKD patients	27/24 (52.9/47.1)	17/31 (35.4/64.6)	21/27 (43.75/56.25)
Stage 5 CKD patients	26/15 (63.4/36.6)	8/13 (38.1/61.9)	4/17(19.1/80.9)
Total	94/66 (58.8/41.2)	54/83 (39.9/60.1)	66/68 (49.3/50.7)

**P*=0.690, ***P*=0.858, ****P*=0.001, *CKD: Chronic kidney disease, HbA1c: Hemoglobin A1c, KDOQI: Kidney Disease Outcomes Quality Initiative*

Table 4: Treatment options of diabetes mellitus according to different stages of chronic kidney disease

Variable	***Diet only***	***Insulin***	***Oral antidiabetic***	***Insulin and oral antidiabetic***
Stage 3a CKD patients	0	5	8	2
Stage 3b CKD patients	0	27	22	4
Stage 4 CKD patients	0	39	8	4
Stage 5 CKD patients	2	36	3	0
Total number (%)	2 (1.25)	107 (66.8)	41 (25.6)	10 (6.25)

CKD: Chronic kidney disease

Discussion

To our knowledge, this was the first study to evaluate multiple treatment goals in CKD patients with DM. In this study, the best compatibility rates to the goals of treatment modalities according to some criteria of the KDOQI 2012 guideline recommendations were found as: the target HbA1c levels recommended should be kept around 7%, BP levels should be equal or less than 130/80 mmHg, and finally the recommendation on the usage of statin or statin/ezetimib combination in CKD patients with DM not on dialysis, respectively.

The first treatment goal evaluated by HbA1c levels to be approximately 7% was almost

achieved in stages 3a, 3b and 5 CKD patients, and although not significant, HbA1c levels were found to be higher in stage 4 patients (Table 2). Total compliance rate to hyperglycemia treatment was 58.8%. According to this result, it can be speculated that as the stage of disease increases, the compatibility to hyperglycemia treatment is worsened, and vice versa. It is well known that HbA1c is one of the major factors leading to decline in GFR in CKD patients with DM (13, 14). In our study, in stage 5 CKD patients HbA1c was found lower because of the decrease in insulin clearance in ESRD patients. A population-based cohort study on glycemic control in people with CKD and DM (13) reported that Hba1c levels higher than 9% in non-hemodialysis-dependent CKD patients was associated with worse clinical outcomes, and HbA1c levels lower than 6.5% were also associated with excess mortality. Additionally, the magnitude of HbA1c-associated ESRD development risk is higher in the early stages of CKD than the advanced stages (13). In another study, type 2 DM patients were divided into two groups according to annual eGFR decline rates as rapid and non-decliners, and it was found that the patients whose HbA1c levels were equal or higher than 7% and had longer duration of DM were associated with rapid annual eGFR decline (14). Because the higher and lower levels of HbA1C are associated with poor clinical outcomes in CKD patients, it is important to keep HbA1c levels around 7%. In our study, the compliance rate to hyperglycemia treatment goal was almost 60% which could be considered successful, compared to the glycemic control rates in a nationwide, multicenter survey of diabetic adult population in Turkey, reporting that HbA1c levels were 8.6±1.9% (71±22 mmol/mol) and 7.7±1.7% (61±19 mmol/mol) in those with type 1 and type 2 DM respectively, and glycemic control was achieved in 15.3% of type 1 and 40.2% of type 2 DM patients (15). The glycemic control rate was found as 32.6%, and the overall control rate for hyperglycemia, hypertension, and dyslipidemia was 11.2% in 9065 patients with type 2 DM (16). A limitation of our study was that because of the retrospective design, we could not detect and evaluate hypoglycemia in our patients.

Another important factor in the progression and development of CKD is hypertension. On the other hand, a decline in kidney function may deteriorate BP control (17, 18). As the CKD stages increase, the compliance rates decrease. In this study, the compatibility rate to hypertension treatment goal in our patients was 49.3%, and we also found a negative relationship between CKD stages and compatibility rates. In a cohort study of 3612 CKD patients, 67% of the patients reached BP goal of <140/90 mmHg (19). A multicenter study about the cardiovascular co-morbidity in CKD and DM patients stated that 53% of patients had hypertension, and only 64% of patients with hypertension had received anti-hypertensive medication. In this study, only 31% of patients reached systolic target while 69% of patients reached diastolic target (20). Treatment-resistant hypertension was found in 33% of CKD patients with DM (21).

The least success rate was found in dyslipidemia treatment. Most of the patients (60.1%) used no statins for cardiovascular prevention, and similar results were observed in previous studies (22, 23). This may be because of unawareness and unwillingness of the physicians to prescribe drugs for CKD patients and incompliance of the patients because of polypharmacy (22, 24). Another reason for the incompliance to statin treatment may be caused by campaign and perception against the use of statins on media.

Conclusion

The treatment goal for hyperglycemia was achieved more successfully, compared to hypertension and dyslipidemia treatment goals in patients with CKD and DM. The small number of patients, and single center experience are the limitations of the study. Further prospective studies with larger sample size are needed.

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Ethical Considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

Conflicts of interest

The authors declare that there is no conflict of interest.

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