ORIGINAL ARTICLE

Dose adjustment of antidiabetic medications in chronic kidney disease

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ABSTRACT

Purpose: The purpose of this study is to identify whether Internal Medicine house-staff (IMHS) have awareness and knowledge about the correct dosage of antidiabetic medications for patients with chronic kidney disease (CKD), as dosing errors result in adverse patient outcomes for those with diabetes mellitus (DM) and CKD. **Methods:** There were 353 IMHS surveyed to evaluate incorrect level of awareness of medication dose adjustment in patients with CKD (ILA) and incorrect level of knowledge of glomerular filtration rate level for medication adjustment (ILK-GFR) for Glipizide, Pioglitazone, and Sitagliptin. **Results:** Lack of awareness and knowledge was high, with the highest for Pioglitazone at 72.8%. For ILA, the percentages were: Pioglitazone: 72.8%, Glipizide: 43.9%, and Sitagliptin: 42.8%. For ILK-GFR, the percentages were: Pioglitazone: 72.8%, Glipizide: 68.3%, and Sitagliptin: 65.4%. **Conclusions:** IMHS have poor awareness and knowledge for antidiabetic medication dose adjustment in patients with DM and CKD. Both Electronic Medical Rerecord best practice advisory and physician–pharmacist collaborative drug therapy management can enhance safe drug prescribing in patients with CKD. In addition, IMHS's practice for antidiabetic medication dose adjustment was better with Nephrology exposure. A formal didactic educational training during medical school and residency for antidiabetic medication dose adjustment in patients with DM and CKD is highly encouraged to prevent medication dosing errors and to more effectively and safely allow IMHS to manage complex treatment regimens.

Key words: Adult-onset diabetes mellitus, chronic kidney insufficiency, internal medicine, medication error, residency and internship

INTRODUCTION

CKD is a global public health problem and in the United States it affects more than 30 million people.[1,2] DM is a leading risk factor for CKD in the United States.[1] Patients with DM often use multiple medications to achieve glycemic control and manage their comorbidities.[3] Patients with CKD, DM, and particularly elderly patients with DM are at high risk for adverse drug events (ADEs) from polypharmacy due to the altered pharmacokinetics of parent drugs and their metabolites.[4,5]

A common cause of dose-related ADEs is failure to properly adjust doses for renal dysfunction.[6] Almost half of the patients with DM and CKD are treated only by primary care physicians (PCPs), with a small number of patients being comanaged by either endocrinologists or nephrologists.[7] Half of all ADEs/ADE-related hospitalizations can be prevented by avoiding inappropriate prescribing from

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PCPs.[8] Inappropriate dose prescribing also includes medication dose modifications done by the hospital medicine team, often Internal Medicine residency trainees and graduates, on patient discharge and before patients being seen by their PCPs.[9]

There does not appear to be any research about whether IMHS possess the necessary awareness and knowledge to prescribe the correct doses of antidiabetic medications in patients with CKD. This study reports percentages for incorrect level of awareness for antidiabetic medication dose adjustment in patients with CKD (ILA) and also incorrect level of knowledge of ILK-GFR for Glipizide, Pioglitazone, and Sitagliptin in patients with impaired renal function. This study conducts exploratory analyses to determine potential variables associated with this incorrect awareness and knowledge.

METHODS

There were 353 IMHS anonymously surveyed to assess awareness and knowledge for dosage adjustment of commonly used diabetes medications in patients with DM and CKD. IMHS are those resident physician trainees that have obtained either an MD, DO, or MBBS degree. Survey sites were six hospitals located in the New York City metropolitan area. The survey was distributed and collected at all hospitals before the beginning of an IMHS conference. IMHS were included across all levels of training. The study received IRB approval. All participants provided informed consent.

Demographic variables were age (years), sex, training level (PGY1, PGY2, PGY3 or greater), and medical school graduate type (U.S. allopathic, U.S. osteopathic, international medical school with U.S. clinical rotation, international medical school without U.S. clinical rotation). The kidney disease history variable consisted of the presence of previous kidney problems among oneself, one's children, or significant other or any first-degree relatives. There were a few variables about increased Nephrology exposure and consisted of renal clinic experience of 10 or more times attending a renal clinic as part of training, participating in a Nephrology rotation in medical school, participating in a Nephrology rotation in medical residency, and interest in studying and training in Nephrology in the future.

We included the diabetes medications that were more commonly prescribed by our hospital's pharmacy. These medications were Glipizide, Pioglitazone, and Sitagliptin. Participants could choose to respond with the options listed later for each diabetes medication. Diabetes medication (1) does not need dose adjustment, (2) needs dose adjustment at glomerular filtration rate (GFR) <90 mL/min, (3) needs dose adjustment at GFR<60 mL/min, (4) needs dose adjustment at GFR <30 mL/min, and (5) I do not know.

We had two different outcomes for the IMHS. One of the outcomes was to measure awareness for whether the diabetes medication dose needed to be adjusted in the setting of compromised renal function ["incorrect level of awareness of medication dose adjustment in patients with CKD (ILA)"]. The other outcome was to measure knowledge for whether IMHS were knowledgeable about the level of GFR that a specific medication for diabetes needed to be adjusted ["incorrect level of knowledge of glomerular filtration rate level for medication adjustment in patients with CKD (ILK-GFR)"]. This knowledge was based on the guidelines from the Physicians' Desk Reference for dosing these diabetes medications when treating patients with CKD.[10] The Physicians' Desk Reference compiles complete United States Food and Drug Administration approved drug label information.

Statistical analysis

Descriptive statistics were used with mean and standard deviation for the continuous variables and frequency and percentage for the categorical variables. Exploratory multivariate logistic regression analyses were conducted with the two different outcomes of ILA and ILK-GFR. Predictors for these analyses included demographics (age, sex), training characteristics (residency training level, type of physician training), kidney disease personal/family history, clinical training (renal clinic, Nephrology rotation in medical school, Nephrology rotation in residency), and further interest in Nephrology training. IBM SPSS Statistics Version 22 was used for all analyses. All p-values were two-sided.

RESULTS

The sample characteristics are described in Table 1. Mean participant age was somewhat older than 29 years. The sample had slightly less women. PGY2 and PGY3 and greater each comprised approximately one-quarter. Almost half consisted of international with U.S. clinical rotation or international without U.S. clinical rotation. For kidney disease history and participation substantially in renal clinics, they were each reported by slightly more than one-tenth. Both Nephrology rotation in medical school and Nephrology rotation in residency were reported by slightly more than one-quarter. Almost one-quarter had further training interest in Nephrology.

Figure 1 shows percentages for perception of ILA and ILK-GFR. For ILA, both Glipizide and Sitagliptin were above 40% whereas Pioglitazone was above 70%. For ILK-GFR, Pioglitazone had the same percentage whereas both Glipizide and Sitagliptin increased to greater than 60%.

Table 2 shows exploratory multivariate logistic regression analyses for ILA. For Glipizide, women had statistically significant higher odds as compared with men for incorrect medication dose needs adjustment. PGY1 had statistically significant higher odds as compared with the reference group of PGY3 and greater for incorrect medication dose needs adjustment. For Pioglitazone, PGY2 had statistically significant higher odds as compared with the reference group of PGY3 and greater for incorrect medication dose needs adjustment. Those with schooling of international with U.S. clinical rotation had statistically significant lower odds as compared with the reference group of U.S. allopathy for incorrect medication dose needs adjustment. For Sitagliptin, women had statistically significant lower odds as compared with men for incorrect medication dose needs adjustment. PGY1 had statistically significant higher odds as compared with the reference group of PGY3 and greater for incorrect medication dose needs adjustment. Those with international schooling with U.S. clinical rotation had statistically significant higher odds as compared with the reference group of U.S. allopathy for incorrect medication dose needs adjustment. Those with a nephrology rotation during residency had statistically significant lower odds for incorrect medication dose needs adjustment.

Table 3 shows exploratory multivariate logistic regression analyses for ILK-GFR. For Glipizide, PGY1 had statistically significant higher odds as compared with the reference group of PGY3 and greater for incorrect medication dose needs adjustment at appropriate GFR level. Those with international schooling without U.S. clinical rotation had statistically significant higher odds as compared with the reference group of U.S. allopathy for incorrect medication dose needs adjustment at appropriate GFR level. Those with a nephrology rotation during medical school had statistically significant lower odds for incorrect medication dose needs adjustment at appropriate GFR level. For Pioglitazone, PGY2 had statistically significant higher odds as compared with the reference group of PGY3 and greater for incorrect medication dose needs adjustment at appropriate GFR level. Also, those with international schooling with U.S. clinical rotation had statistically significant lower odds as compared with the reference group of U.S. allopathy for incorrect medication dose needs adjustment at appropriate GFR level. For Sitagliptin, PGY1 had statistically significant higher odds as compared with the reference group of PGY3 and greater for incorrect medication dose needs adjustment at appropriate GFR level. Those with a kidney disease history had statistically significant lower odds for incorrect medication dose needs adjustment at appropriate GFR level.

Table 1: Descriptive statistics of a sample of 353 internal medicine house-staff

Variables	Frequency or mean	Percent or SD
Age (years) [mean]	29.2	2.95
Sex		
Men	184	52.1
Women	159	45.0
Missing	10	2.8
Training		
PGY1	158	44.8
PGY2	101	28.6
PGY3 and greater	82	23.2
Missing	12	3.4
School		
U.S. allopathic	123	34.8
U.S. osteopathic	42	11.9
International with U.S. clinical rotation	109	30.9
International without U.S. clinical rotation	61	17.3
Missing	18	5.1
Kidney disease history (yes)	38	10.8
Missing	9	2.5
Renal clinic (yes)	38	10.8
Missing	12	3.4
Nephrology rotation medical school (yes)	100	28.3
Missing	13	3.7
Nephrology rotation residency (yes)	96	27.2
Missing	9	2.5
Nephrology further training interest (yes)	79	22.4
Missing	15	4.2

Note: SD = standard deviation. Sex above adds up to 99.99% due to rounding to one decimal point. Precise percentages to total 100% are: men: 52.1246%, women: 45.0425%, and missing: 2.8329%.

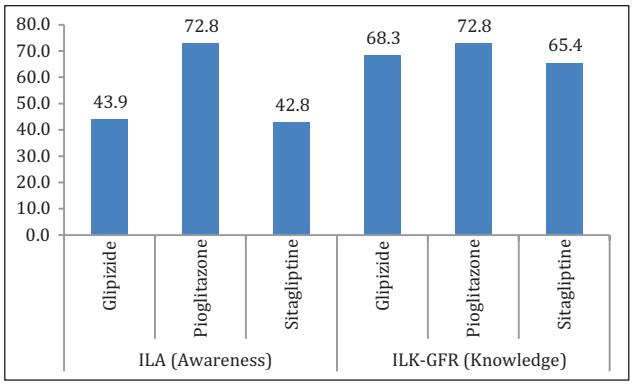

Figure 1: Percentages for incorrect level of awareness of medication dose needs adjustment (ILA) and incorrect level of knowledge of medication dose needs adjustment at appropriate GFR level (ILK-GFR) for diabetes medications

Table 2: Multivariate logistic regression analyses for incorrect level of awareness of medication dose needs adjustment

Variables	GLI OR	95% CI	*P*-value	PIO OR	95% CI	*P*-value	SIT OR	95% CI	*P*-value
Age (years)	1.00	0.91, 1.11	*0.93*	0.97	0.87, 1.07	*0.51*	1.02	0.93, 1.12	*0.73*
Sex (women)	**1.73**	**1.03, 2.91**	***0.04***	1.18	0.65, 2.14	*0.59*	**0.56**	**0.33, 0.95**	***0.03***
Training									
PGY3 and greater	Reference group			Reference group			Reference group		
PGY1	**4.55**	**2.19, 9.45**	***<0.001***	1.98	0.97, 4.06	*0.06*	**3.06**	**1.52, 6.14**	***0.002***
PGY2	2.05	0.94, 4.46	*0.07*	**2.33**	**1.05, 5.14**	***0.04***	1.54	0.74, 3.24	*0.25*
School									
U.S. allopathic	Reference group			Reference group			Reference group		
U.S. osteopathic	1.64	0.70, 3.84	*0.25*	0.40	0.16, 1.03	*0.06*	1.68	0.74, 3.84	*0.22*
International with U.S. clinical rotation	0.91	0.47, 1.75	*0.78*	**0.39**	**0.19, 0.80**	***0.01***	**2.59**	**1.35, 4.97**	***0.004***
International without U.S. clinical rotation	1.60	0.72, 3.55	*0.25*	0.85	0.33, 2.17	*0.73*	1.46	0.66, 3.24	*0.36*
Kidney disease history	1.07	0.45, 2.52	*0.88*	1.44	0.51, 4.09	*0.50*	0.50	0.21, 1.21	*0.12*
Renal clinic	0.50	0.19, 1.32	*0.16*	1.28	0.44, 3.67	*0.65*	0.63	0.25, 1.61	*0.33*
Nephrology rotation medical school	0.88	0.48, 1.60	*0.68*	1.21	0.62, 2.37	*0.57*	0.77	0.43, 1.37	*0.37*
Nephrology rotation residency	0.69	0.38, 1.24	*0.21*	1.01	0.52, 1.96	*0.97*	**0.56**	**0.31, 0.998**	***0.049***
Nephrology further training interest	1.36	0.72, 2.56	*0.35*	1.56	0.73, 3.34	*0.25*	0.92	0.50, 1.71	*0.79*

Values that are bold/italics are those that are statistically significant

Note: GLI = Glipizide, PIO = Pioglitazone, SIT = Sitagliptin, OR = odds ratio, CI = confidence interval

Table 3: Multivariate logistic regression analyses for incorrect level of knowledge of medication dose needs adjustment at appropriate GFR level

Variables	GLI OR	95% CI	*p-value*	PIO OR	95% CI	*p-value*	SIT OR	95% CI	*p-value*
Age (years)	0.96	0.87, 1.06	*0.40*	0.97	0.87, 1.07	*0.51*	1.00	0.91, 1.10	*0.96*
Sex (women)	1.42	0.81, 2.51	*0.22*	1.18	0.65, 2.14	*0.59*	0.79	0.46, 1.34	*0.37*
Training									
PGY3 and greater	Reference group			Reference group			Reference group		
PGY1	**2.53**	**1.23, 5.23**	***0.01***	1.98	0.97, 4.06	*0.06*	**2.32**	**1.17. 4.61**	***0.02***
PGY2	1.24	0.60, 2.55	*0.57*	**2.33**	**1.05, 5.14**	***0.04***	1.36	0.68, 2.72	*0.39*
School									
U.S. allopathic	Reference group			Reference group			Reference group		
U.S. osteopathic	1.27	0.51, 3.11	*0.61*	0.40	0.16, 1.03	*0.06*	1.28	0.55, 2.98	*0.57*
International with U.S. clinical rotation	1.91	0.94, 3.87	*0.07*	**0.39**	**0.19, 0.80**	***0.01***	1.70	0.88, 3.31	*0.12*
International without U.S. clinical rotation	**3.13**	**1.26, 7.77**	***0.01***	0.85	0.33, 2.17	*0.73*	1.97	0.86, 4.50	*0.11*
Kidney disease history	1.94	0.72, 5.22	*0.19*	1.44	0.51, 4.09	*0.50*	**0.43**	**0.19, 0.97**	***0.04***
Renal clinic	0.77	0.30, 1.99	*0.59*	1.28	0.44, 3.67	*0.65*	0.74	0.30, 1.83	*0.52*
Nephrology rotation medical school	**0.52**	**0.28, 0.97**	***0.04***	1.21	0.62, 2.37	*0.57*	0.61	0.34, 1.09	*0.10*
Nephrology rotation residency	0.73	0.40, 1.35	*0.32*	1.01	0.52, 1.96	*0.97*	0.81	0.45, 1.43	*0.46*
Nephrology further training interest	1.75	0.84, 3.65	*0.14*	1.56	0.73, 3.34	*0.25*	1.01	0.53, 1.92	*0.99*

Values that are bold/italics are those that are statistically significant

Note: GLI = Glipizide, PIO = Pioglitazone, SIT = Sitagliptin, OR = odds ratio, CI = confidence interval

DISCUSSION

This study found that there were high percentages and high odds for incorrect level of awareness of medication dose adjustment in patients with CKD (ILA) and incorrect level of knowledge of ILK-GFR in patients with CKD for Glipizide, Pioglitazone, and Sitagliptin among IMHS [see Figure 1]. Exploratory analyses for antidiabetic medications showed that PGY1 and PGY2 had higher odds for both ILA and ILK-GFR. Graduates of international medical schools without U.S. clinical rotations had higher odds for ILK-GFR for Glipizide. IMHS with greater exposure to nephrology (i.e. Nephrology rotation in medical school or residency and personal/family history of kidney disease) had lower odds

of ILA or ILK-GFR. Women and graduates of international medical schools with U.S. clinical rotations had mixed patterns for ILA or ILK-GFR. Women had higher odds for ILA with Glipizide but lower odds for ILA with Sitagliptin. Graduates of international medical schools with U.S. clinical rotations had higher odds for ILA with Sitagliptin but lower odds for ILA and ILK-GFR with Pioglitazone.

ILA and ILK-GFR were highest in Pioglitazone, with almost three-quarters of IMHS responding incorrectly to dose adjustments. For Glipizide and Sitagliptin, almost half of IMHS responded incorrectly to dose adjustments for ILA and about two-thirds for ILK-GFR. The current study results are similar to international findings, which showed that prescribers did not make adequate drug dose adjustments for two-thirds of antidiabetic medications and in 29–74% of patients with renal impairment.[11,12] Recently, some European and many South Asian countries suspended Pioglitazone use due its adverse side-effect profile.[13] This could have led to decreased focus on education about Pioglitazone and, consequently, decreased awareness and knowledge among the IMHS that trained or worked in these countries. Glipizide is a well-established antidiabetic medication with recognized deleterious side-effects of hypoglycemia and weight gain.[14] As Sitagliptin is a relatively new medication with a better and safer side-effect profile,[14,15] more robust efforts were provided to educate clinicians about its use.[16] These medication attributes likely resulted in greater didactic focus and may have been the reason for the somewhat improved awareness and knowledge, although overall both were still quite poor. One potential explanation for the overall poor awareness and knowledge for dose adjusting among IMHS is didactic emphasis on use of antidiabetic medications in the general DM population rather than in those with CKD.[17]

To improve patient safety, it is important to implement strategies to prevent medication dosing errors. Having additional nephrology education either in medical school or in residency is associated with improved level of awareness and knowledge among IMHS.[18] Both internal medicine residents and PCPs have gaps in their knowledge of CKD practice guidelines and treatment of CKD complications.[19] Improved education of CKD among training physicians can result in improved patient care and clinical outcomes.[18] This may come in the form of additional ambulatory Nephrology exposure as conditions such as CKD are best taught in the outpatient setting.[20]

Another strategy to improve patient safety and quality of patient care is to implement an Electronic Medical Record (EMR) best practice advisory. As EMR is now being widely adopted across the United States, it provides a unique opportunity to minimize dosing errors by supporting enhanced adherence to clinical dosing guidelines in both inpatient and outpatient settings.[21] The EMR can support a complex, dynamic, medical decision-making process that results in improved medication management by enabling more accurate, comprehensive, and automated medication prescribing and delivery.[22] In addition to improving medication documentation, identification of patients affected by a drug recall, and managing prescriptions for controlled drugs more effectively, the EMR advisory can identify and flag drug interactions, and ensure appropriate and safe drug prescribing for the level of CKD.[23]

Pharmacist support provides another level of enhanced patient safety and medication dosing optimization in patients with CKD.[24] Pharmacists integrated in ambulatory care reduce hospitalizations by more than 20%, resulting in significant cost savings per patient.[25] Despite the overwhelmingly positive impact of pharmacist services on patient outcomes, the integration of pharmacists in ambulatory care programs is not widespread. This is a missed opportunity as collaborative care between pharmacists and physicians improves pharmacotherapeutic outcomes and provides increased value and efficiency to the health-care system.[24] The three types of pharmacist collaborative care models: (1) a pharmacist with physician oversight, (2) pharmacist–interprofessional teams, and (3) physician–pharmacist teams that are being suggested for physician–pharmacist collaborative drug therapy management have demonstrated the positive impact in patients with chronic conditions, including DM and CKD.[24]

The data from our study are very similar to data reported from IMHS training in the United States and, therefore, can be generalizable. In a report for those training in the 2015–2016 academic year, the ACGME reported that 24,983 IMHS participated in training in the United States.[26] Our study reported a mean age of 29.2 years and with a sex representation at 45% from females. Our study is similar to the data reported from the U.S. national training data of IMHS with a mean age of 29.3 years and with a sex representation at 41% from females.[26] Our sample from New York State reported 48.2% IMGS, which is similar to the ACGME report of 41.2% IMGs for the whole New York State and 40.0% throughout the United States.[26] The training level from our sample for each level of training is similar to the statistics overall in the United States: 44.8% current sample versus 39.9% U.S. national for PGY1 trainees, 28.6% current

sample versus 30.7% U.S. national for PGY2 trainees, and 23.2% current sample versus 29.4% U.S. national for PGY3 trainees.[26]

A strength of our study is that we did not allow the physicians participating to use computer-based or cellular-phone-based apps or programs to assist in answering our survey questions about prescription dose adjustment and thus we are best measuring physician awareness and knowledge. We agree that these apps and programs are potentially available in clinical practice. However, physicians are busy and typically do not often use these apps and programs.[27] The study has several limitations. First, our study is from one geographic area and may not generalize to other areas. Second, we chose medications based on what diabetes medications are often prescribed at our institution. Each institution may have different preferences for the medications used to treat diabetes. Third, we did not include Endocrinology rotation as a variable. It is possible that an Endocrinology rotation could be comparable to Nephrology rotation with the exposure to a daily prescription of antidiabetic medications. Fourth, it is also possible that results might slightly differ if someone had more than one exposure from the three Nephrology clinical training variables. Fifth, there is the possibility of recall bias in the self-reported survey responses.

In conclusion, there was an overall poor awareness and knowledge among IMHS for proper dose adjustments with antidiabetic medications in patients with CKD. Poor knowledge of renal dosing guidelines has been identified as a major cause of prescribing errors and the resulting morbidity and occasionally mortality.[6,8] It appears that current medical education and training has deficiencies in the area of medication dose adjustment for renal dysfunction, thus potentially negatively impacting patient safety. Both EMR best practice advisory and physician–pharmacist collaborative drug therapy management can improve patient safety by appropriate adjustment of medications in patients with CKD. The role of PCPs in the management of patients with DM and CKD is becoming more essential due to the increasing prevalence of both DM and CKD.[2,6] As PCPs prescribe the majority of antidiabetic medications, it is essential that IMHS receive more Nephrology clinical exposure and formal didactic educational training during residency for dose adjustment in patients with CKD. This can ensure appropriate and safe prescribing.

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Conflicts of interest
None of the authors have any conflict of interest.

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