Clinical Kidney Journal

ckj

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Leading European Nephrology

Clinical Kidney Journal, 2017, vol. 10, no. 5, 661–665

doi: 10.1093/ckj/sfx020
Advance Access Publication Date: 25 May 2017
Original Article

ORIGINAL ARTICLE

Changes in treatment of hyperglycemia in a hypertensive type 2 diabetes population as renal function declines

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Abstract

Background: Cardiovascular complications associated with expensive noninsulin agents for type 2 diabetes are the focus of concern in light of the risk of kidney dysfunction with aging. Head-to-head comparisons are unavailable to guide the choice of new drugs for hyperglycemia in patients with type 2 diabetes, decreased estimated glomerular filtration rate (eGFR) and increased cardiovascular risk. A first approach would be to document current medication choices.

Methods: All prescriptions for 10 151 patients (5623 males/4528 females) with both type 2 diabetes and hypertension seen two or more times during a 5-year period (2007–12) at Joslin Diabetes Center were evaluated. {mean age 64 years [interquartile range (IQR) 64–65)], body mass index 31 kg/m^2 (IQR 30–32) and mean eGFR 78 mL/min/1.73 m^2 (IQR 78, 78)}.

Results: Insulin was used in >60% of patients, metformin in 50% and sulfonylurea derivatives in 25%. Dipeptidyl peptidase 4 (DPP4) and acarbose class drugs were prescribed in 10% of patients, GLP-1 in 8% and other classes [including thiazolidinediones (TZD)] in <5%. Patients were grouped into four drug **Categories** none, 447 (4%); insulin only, 3836 (38%); other than insulin, 2910 (29%) and insulin combinations, 2955 (29%). Common combinations included insulin/metformin [$n = 2493$ (25%)], insulin/sulfonylureas [706 (7%)], metformin/sulfonylureas [2017 (20%)], metformin/GLP1 [949 (9%)], metformin/DPP4 [895 (9%)] and metformin/TZD [500 (5%)]. Insulin use increased to 70% from 35% as eGFR dropped to <30 mL/min/1.73 m^2; use of insulin combined with other drugs dropped to 12% from 31% and the use of other drugs alone without insulin dropped similarly to 12% from 30%.

Conclusions: Reduced renal function was associated with increased use of insulin and decreased use of other anti-diabetic agents in a statistically significant progression. BMI and gender did not influence medication choice.

Key words: cardiovascular, CKD, hypertension, insulin, type 2 diabetes

Received: October 5, 2016. **Editorial decision:** February 27, 2017

Introduction

Despite continued efforts to control hemoglobin A1c (HbA1c) and an ever-expanding arsenal of new drugs [1], we may fall short of adequate control in a significant portion of patients with diabetes due to failure to recognize comorbidities [2]. As kidney disease progresses, clearance of oral agents such as glyburide, metformin or sitagliptan may be so diminished as to require discontinuation. The decrease in renal function due to acute kidney injury and chronic kidney disease (CKD) exacerbates fluid/volume overload, congestive heart failure, high blood pressure [3] as well as other comorbidities. Since there is little data focusing on the impact of renal dysfunction on these therapeutic choices, we examined the effect of renal (dys)function on the choice of antidiabetic medications.

Materials and methods

To understand the medication decisions in patients with both type 2 diabetes and hypertension, we evaluated the records of all patients seen at least twice during a sample 5-year period at Joslin Diabetes Center. This study was approved by the Committee on Human Studies of the Joslin Diabetes Center as a quality assurance study to determine adherence to quality guidelines. All patient records were anonymized and patient data deidentified prior to analysis. During this time 15 481 patients were seen more than twice and 10 540 individuals had diagnosis codes for both hypertension and diabetes. Of these 10 151 patients were identified as meeting these criteria with complete demographic information regarding height, weight, body mass index (BMI), estimated glomerular filtration rate (eGFR) and medication records available. There were 5623 men and 4528 women with a mean BMI of 31 kg/m^2 (men 30, women 32), height 67 inches (69, 63), weight 198 lb (212, 182) and mean eGFR of 78 mL/min/1.73 m^2 (78, 78). Ninety percent of patients received lipid-lowering medications [statins 78 (73%)] and 60% (63, 60) also received aspirin. Demographic data stratified by the baseline level of renal function are included in Table 1.

Listed also in Table 1 are the individual antidiabetic medication prescriptions for the 10 151 patients. Insulin was used in >60% of patients, metformin in 50% and sulfonylurea derivatives in 25%. Dipeptidyl peptidase 4 (DPP4) inhibitors and acarbose (alpha-glucosidase inhibitors) were prescribed in 10%, glucagon-like peptide-1 (GLP-1)) receptor agonists in 8% and other classes [including thiazolidinediones (TZD)] in <5%. Common combinations included insulin/metformin [2493 (25%)], insulin/sulfonylureas [706 (7%)], metformin/sulfonylureas [2017 (20%)], metformin/GLP1 [949 (9%)] metformin/DPP4 [895 (9%)] and metformin/TZD [500 (5%)].

To analyze the relationship between levels of renal function and strategies aimed at diabetes control, we prespecified levels of renal dysfunction based on standard definitions into

Table 1. Data for 10 151 patients with complete demographic and medication data identified as having hypertension and type 2 diabetes by eGFR categories from the Joslin Diabetes Center

Characteristics	eGFR < 30 (n = 565)	eGFR 30–60 (n = 2230)	eGFR 60–90 (n = 3924)	eGFR > 90 (n = 3432)	P-value for trend
Age, years, mean (95% CI)	71.0 (60.0–79.0)	73.0 (66.0–81.0)	67.0 (59.0–74.0)	57.0 (49.0–64.0)	<0.001
Sex, male, n (%)	293 (51.9)	1116 (50.0)	2090 (53.3)	2124 (61.9)	<0.001
HT, inches, mean (95% CI)	66.0 (63.0–69.0)	66.0 (63.0–69.0)	67.0 (63.8–70.0)	68.0 (65.0–70.5)	<0.001
WT, lbs, mean (95% CI)	186.0 (154.8–220.6)	190.0 (162.0–224.0)	192.0 (163.6–224.0)	198.0 (170.0–231.0)	<0.001
BMI, mean (95% CI)	29.9 (25.3–35.0)	30.4 (26.6–35.3)	30.1 (26.3–34.5)	30.2 (26.6–34.9)	0.52
eGFR, mg/dL, mean (95% CI)	21.4 (13.9–25.7)	48.1 (41.2–54.6)	76.3 (68.6–81.9)	105.6 (96.7–120.0)	<0.001
Medication category, n (%)					
No meds	38 (6.7)	125 (5.6)	179 (4.6)	128 (3.7)	<0.001
1 Med	442 (78.2)	1228 (55.1)	1850 (47.1)	1715 (50.0)	
2 Meds	66 (11.7)	612 (27.4)	1250 (31.9)	975 (28.4)	
3 Meds	16 (2.8)	226 (10.1)	538 (13.7)	523 (15.2)	
>3 Meds	3 (0.5)	39 (1.7)	107 (2.7)	91 (2.7)	
Statin, n (%)	421 (74.5)	1810 (81.2)	3029 (77.2)	2446 (71.3)	<0.001
Nonstatin, n (%)	68 (12.0)	279 (12.5)	365 (9.3)	256 (7.5)	<0.001
Aspirin, n (%)	358 (63.4)	1524 (68.3)	2462 (62.7)	1741 (50.7)	<0.001
Insulin, n(%)	462 (81.8)	1563 (70.1)	2469 (62.9)	2297 (66.9)	<0.001
Insulin only, n (%)	396 (70.1)	955 (42.8)	1267 (32.3)	1218 (35.5)	<0.001
Other than insulin, n (%)	65 (11.5)	547 (24.5)	1283 (32.7)	1015 (29.6)	<0.001
Insulin and other, n (%)	66 (11.7)	608 (27.3)	1202 (30.6)	1079 (31.4)	<0.001
Metformin, n (%)	8 (1.4)	642 (28.8)	2128 (54.2)	1891 (55.1)	<0.001
Sulfonylurea, n (%)	98 (17.3)	625 (28.0)	1033 (26.3)	820 (23.9)	0.62
Thiazolidinedione, n (%)	11 (1.9)	83 (3.7)	101 (2.6)	73 (2.1)	0.018
DPP4 inhibitor, n (%)	38 (6.7)	257 (11.5)	382 (9.7)	235 (6.8)	<0.001
Acarbose, n (%)	2 (0.4)	11 (0.5)	16 (0.4)	27 (0.8)	0.08
Nateglinide, n (%)	1 (0.2)	3 (0.1)	7 (0.2)	3 (0.1)	0.53
Repaglinde, n (%)	9 (1.6)	34 (1.5)	59 (1.5)	31 (0.9)	0.03
Pramlintide, n (%)	3 (0.5)	15 (0.7)	36 (0.9)	54 (1.6)	0.004
GLP-1 inhibitor, n (%)	2 (0.4)	54 (2.4)	169 (4.3)	170 (5.0)	<0.001

Sulfonylurea drugs: glipizide, glyburide, glimeperide, tolbutamide.
Thiazolidinediones: rosiglitazone, pioglitazone.
DPP4 inhibitors: sitagliptan, linagliptan, saxagliptan.
GLP-1 inhibitors: liraglutide, exenatide.

categories of eGFR by the Modified Diet in Renal Disease (MDRD) equation (4): <30, 30–60, 60–90 and >90 mL/min.

To best describe complex baseline treatment regimens, we analyzed choices of medications in categories defined by insulin usage: no glucoregulating medications, noninsulin agents (any agent other than insulin), insulin only and insulin plus any other agent.

Results

Of the 10 151 patients, 565 (5.6%) had an eGFR <30 mL/min/1.73 m^2, 2230 (22%) 30–60 mL/min, 3924 (38.7%) 60–90 mL/min and 3432 (33.8%) >90 mL/min. Table 1 lists baseline antidiabetic medication stratified by the level of renal function. Patients with Stage 3 or greater renal dysfunction (eGFR < 60 mL/min)/1.73 m^2 were slightly older and more likely to be taking aspirin. BMI and gender did not vary between groups. From the total group it was noted that 470 (4.63% of patients) received no blood glucose–lowering medication, 5235 (51.57%) received one, 2903 (28.60%) two, 1303 (12.84%) three and 240 (2.36%) four or more. Observed in another fashion, noninsulin agents (any agent other than insulin) were used alone in 2910 patients (29% of the total group), insulin was the sole agent in 3836 (38%) and combinations of insulin plus other noninsulin agents were used in 2955 patients (29%).

In groups defined by eGFR <60 mL/min/1.73 m^2, the use of insulin was statistically significantly increased (70.5% versus 64.8%; $P < 0.01$). Similar findings were noted comparing the cohort with eGFR <30 mL/min/1.73 m^2 to all other eGFR cohorts (all $P < 0.01$). Use of noninsulin antidiabetes medications decreased with lower levels of renal function. In groups defined by eGFR <60 mL/min/1.73 m^2, the use of non-insulin medications was statistically significantly decreased (53.8% versus 62.3%; $P < 0.01$). Similar findings were noted comparing the cohort with eGFR <30 mL/min/1.73 m^2 to all other eGFR cohorts (all $P < 0.01$). The decrease in noninsulin antidiabetes medication prescription occurred predominately because of decreased use of metformin.

Discussion

For populations with both type 2 diabetes and hypertension, the choice of antidiabetic medication is driven by clinical guidelines, cost and physician preference. Both diabetes and hypertension guidelines focus on deriving the best benefit:risk ratio based on evidence from clinical trials. Evidence supporting these guidelines is predominantly from biomarkers (blood pressure, HbA1C, weight gain) rather than hard clinical outcomes data [4]. For many antidiabetic and antihypertensive trials, the population with marked renal dysfunction is underrepresented or excluded. Our findings suggest that prescriptions for the management of diabetes are influenced by the level of renal function and not by gender or BMI. However, the impact of BMI on treatment choice requires further study, as the number of antidiabetic agents that may assist with weight loss has grown since this population was evaluated [5].

Clinicians are often faced with an overweight, hypertensive, type 2 diabetic patient for whom dietary control, weight loss and exercise have failed to control glycohemoglobin. Advances in antidiabetic therapy have given us multiple medications with different metabolic profiles. For each of these, however, there are limited data on long-term outcome and we thus focus on the reduction of biomarkers (HbA1C, blood pressure). As duration, end organ damage and severity of diabetes and/or hypertension increase, the burden of multiple medications and drug–drug interactions increases. Renal dysfunction, with its higher incidence of associated cardiovascular disease, also changes drug metabolism, dosage, side-effect profiles and ultimately our strategies for pharmacologic intervention. Yet, as these populations are often excluded from major trials, no outcomes data are available upon which to base appropriate decisions.

Guidelines do not make specific recommendations on the agents to use. The Standards of Medical Care in Diabetes for 2017 abridged for primary care providers simply note that 'with reduced eGFR, drug dosing may require modification'. It reports the US Food and Drug Administration contraindication of using metformin with an eGFR <30 mL/min/1.73 m^2 and recommends not starting the drug in patients with an eGFR <45 mL/min/1.73 m^2 (CKD Stage IIIb). Our data show that metformin use dropped to 28.8% from 54.2% as eGFR dropped below 60 mL/min/1.73 m^2 [6].

European guidelines are more detailed, making specific recommendations on reductions of drug dose by CKD stage. At the same time, the guidelines recommend against tighter glycemic control in patients with eGFR <45 mL/min/1.73 m^2 if this results in severe hypoglycemic episodes and recommend vigilant attempts to tighten glycemic control to bring HbA1c down when it is >8.5% [7].

Most patients diagnosed with type 2 diabetes will ultimately be determined to be hypertensive. With aging, and the onset of macroalbuminuria and/or diminished eGFR, these patients will require antihypertensive therapy to protect renal and retinal function. Multidrug pharmacologic decision making becomes increasingly complex. It is unlikely that antidiabetic medication comparisons similar in design to the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial for antihypertensive agents will be available soon [8]. It is also unlikely that large controlled outcome comparisons of antidiabetic agents will take place in populations with chronic renal insufficiency, particularly since one retrospective study has demonstrated that the use of metformin in very advanced (Stage V) renal failure is associated with increased mortality [9]. Until additional studies are available, we must consider whether current practice differences relate to guidelines, choice, perceived mechanisms of action, cost or the underlying patient population.

In a multinational cooperative study involving >2500 patients from North America and 1500 from Europe, Australia and Latin America it was concluded that North American clinicians employed the most conservative approach to diminishing use of metformin with lower eGFR [10]. The current report from a single-center separate cohort involving a broader range of renal function extends the observation that current prescriptions are influenced by the baseline level of renal function. At an eGFR <30 mL/min/1.73 m^2, data from multiple North American centers indicated 8% utilization of biguanides versus 1.5% in this New England cohort.

As we observe the burden of our treatment decisions for populations with both diabetes and hypertension, we should note that in our cohort the median number of antihypertensive drugs was two, both aspirin and lipid-lowering agents are mandated by guidelines, 29% of patients were on insulin plus an other agent, patients taking insulin only required multiple injections or mixes and patients on oral agents only were often on mixes of oral agents such as metformin and sufonylureas. Few medications used required once-daily dosing.

Although one might consider that less medication would be required with diminished renal function, other issues such as decreased responsiveness to medications (SGLT-2, hydrochlorthiazide), hyperkalemia, drug–drug interaction and

phosphate-binding issues may also increase the burden of treatment [11, 12]. Added to this burden is the comorbidity associated with elevated blood pressure and increased antihypertensive medications with diminished renal reserve [13].

Our observations in a large community-based diabetic hypertensive population suggest that current prescriptions are significantly influenced by the baseline level of renal function and not by gender or BMI. Practicing clinicians appear to recognize that renally excreted drugs have not been demonstrated to improve outcomes in patients with advanced renal insufficiency and possibly in those at risk of changing renal function between visits.

Limitations

This was an observational, cross-sectional study from a single center dedicated to the treatment of diabetes. As such, it may not reflect the care given by centers with a broader focus. No attempt was made to influence treatment. The study was undertaken as part of a quality of care analysis to determine whether a computer dataset could adequately demonstrate the extent to which current evidence-based guidelines were being implemented during a fixed time period. The study was not designed to assess the pathogenesis of type 2 diabetes or renal disease or the adequacy of clinical control of blood pressure, diabetes, lipid or renal management. The study design does not permit assessment of the effectiveness of therapy or health care outcomes associated with individual or combination medication regimens. This study also does not address the frequency of overtreatment with resultant hypoglycemia [13] or the reasons for the use of medications deemed inappropriate for use as renal function declines [14]. During the years since the period analyzed, additional therapies that were either not available or extensively used during the period of our analysis have become popular. An example would be liraglutide, which enhances renal salt removal in hypertensive subjects with type 2 diabetes [15]. Other studies have similar issues in that antidiabetes medications available at the study completion may not have been available at their onset [16]. Recent data regarding DPP4 inhibitors raised concern about excess heart failure in 887 (82% hypertensive) patients exposed to sitagliptan [17–19]. These data were not available at the onset of our analysis. Incident heart failure was not analyzed in this cross-sectional study.

Conclusions

Reduced renal function was associated with increased use of insulin and decreased use of other antidiabetic agents in a statistically significant progression. BMI and gender did not influence medication choice. It is not possible in this descriptive study to examine whether the changes reflected shared decision making by patient and physician. The results do show that prescription patterns were driven by renal function. Future studies are required to specifically determine the best glycemia control strategies for populations with type 2 diabetes, hypertension and diminished renal reserve. This should also include examining whether there are significant changes in glycemic control (hyper or hypo) associated with changes in agents and whether changes in antihyperglycemic agents were significantly associated with similar changes in antihypertensive agents. The choice of antidiabetic agent may be especially important in those patients anticipated to require therapies that may result in either acute or prolonged diminished renal function.

Conflict of interest statement

None declared.

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