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Original Article

Impaired renal function modifies the risk of severe hypoglycaemia among users of insulin but not glyburide: a population-based nested case–control study

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Abstract

Background. Little evidence justifies the avoidance of glyburide in patients with impaired renal function. We aimed to determine if renal function modifies the risk of hypoglycaemia among patients using glyburide.

Methods. We conducted a nested case–control study using administrative records and laboratory data from Ontario, Canada. We included outpatients 66 years of age and older with diabetes mellitus and prescriptions for glyburide, insulin or metformin. We ascertained hypoglycaemic events using administrative records and estimated glomerular filtration rates (eGFR) using serum creatinine concentrations.

Results. From a cohort of 19,620 patients, we identified 204 cases whose eGFR was ≥60 mL/min/1.73 m^2 (normal renal function) and 354 cases whose eGFR was <60 mL/min/1.73 m^2 (impaired renal function). Compared to metformin, glyburide is associated with a greater risk of hypoglycaemia in patients with both normal [adjusted odds ratio (OR) 9.0, 95% confidence interval (95% CI) 4.9–16.4] and impaired renal function (adjusted OR 6.0, 95% CI 3.8–9.5). We observed a similar relationship when comparing insulin to metformin; the risk was greater in patients with normal renal function (adjusted OR 18.7, 95% CI 10.5–33.5) compared to those with impaired renal function (adjusted OR 7.9, 95% CI 5.0–12.4). Tests of interaction showed that among glyburide users, renal function did not significantly modify the risk of hypoglycaemia, but among insulin users, impaired renal function is associated with a lower risk.

Conclusions. In this population-based study, impaired renal function did not augment the risk of hypoglycaemia associated with glyburide use.

Keywords: CKD; glyburide; hypoglycaemia; insulin; metformin

Introduction

Strict glycaemic control is a tenet of diabetes mellitus management because it is associated with improved micro- and macrovascular outcomes [1–8]. Diabetes is the primary aetiology in one quarter of patients with chronic kidney disease (CKD) and about half of those with end-stage renal disease [9,10]. Among patients with established diabetic nephropathy, disease progression can be slowed by controlling blood glucose to near-normal levels [1,4,7,11]. However, this rigorous control is achieved at the expense of an increased rate of hypoglycaemic events [1,7].

The risk of hypoglycaemia is a particular concern among patients with impaired renal function [12]. In these patients, the counter-regulatory response to hypoglycaemia may be limited by impaired renal gluconeogenesis or poor glycogen reserves caused by uraemia-induced anorexia [13–15]. In addition, the clearance of some commonly prescribed diabetes therapies depends on renal function. This is the case for glyburide, the active metabolites of which are slowly eliminated in the setting of impaired renal function [16–20]. Based largely on glyburide's pharmacokinetic data, national treatment guidelines have recommended avoiding its use once the estimated glomerular filtration rate (eGFR) falls below 60 mL/min/1.73 m^2 [21]. However, the body of evidence supporting this recommendation is weak and contradictory [22,23], and the limited clinical data on glyburide's hypoglycaemic potential have arisen from descriptive studies and small observational studies [24–26]. Glyburide remains an effective diabetes therapy that has been used in a trial demonstrating the benefits of strict glycaemic control [1]. Unfortunately, this trial is of little use in understanding glyburide's side-effect profile because, like many trials, it did not include patients with

CKD [27]. Without a clear understanding of the risk glyburide poses to patients with impaired renal function, we cannot adequately assess the appropriateness of its use in this population.

To quantify this risk in a large population-based analysis, we conducted two nested case–control studies using outpatient laboratory data that we linked to Ontario's health administrative data. We designed each study to assess drug-specific hypoglycaemia risks in patients with impaired and normal kidney function. We hypothesized that the risk of severe hypoglycaemic events in patients using glyburide would be greater in those with impaired kidney function compared to those with normal kidney function.

Materials and methods

Study design

We used health administrative databases in Ontario, Canada to establish a nest cohort of patients older than 65 years with diabetes. Within this cohort, we conducted two case–control studies to assess the risk of hypoglycaemia associated with the use of glyburide or insulin as compared to the reference drug, metformin. Two studies were done to explore the interaction between renal function and these diabetes therapies in terms of their hypoglycaemic risks; patients with eGFR values above 60 mL/min/1.73 m^2 were included in the first study, and patients with an eGFR value below this level were included in the second study. To assess interaction, we compared adjusted odds ratios (OR) derived from the two studies. We collected and analysed all exposure, outcome and covariate data according to a predefined protocol. The study was approved by the institutional review board at Sunnybrook Health Sciences Centre, Toronto, Canada, and its design and reporting follow the Strengthening the Reporting of Observational Studies in Epidemiology statement guidelines [28].

Setting and sources of data

We acquired data from 1 January 1997 to 31 March 2008 using the linked health administrative data of Ontario, Canada. Ontario has ~12 million residents, 1.6 million of whom are 65 years of age or older [29]. All Ontario residents receive universal access to physician and hospital services through the Ontario Health Insurance Plan (OHIP). Ontario residents older than 65 years also receive universal formulary coverage for prescription medications through the Ontario Drug Benefits (ODB) programme. Ontario's single health insurance payer and the yearly emigration rate of <1% provide a set of health administrative data that is both comprehensive and stable [30]. We ascertained dispensed prescription medications using the ODB database, which has a basic error rate <1% [31]. We collected data regarding inpatient and outpatient hospital visits from the Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD) and the National Ambulatory Care Reporting System (NACRS) database. These databases contain detailed diagnostic information coded using the ninth and tenth revisions of the International Classification of Disease (ICD-9 and ICD-10). The coding accuracy of these databases has been assessed for many diagnoses [32,33]. We determined kidney function using serum creatinine values obtained from the Gamma-Dynacare laboratory database. Gamma-Dynacare laboratories provide ambulatory blood work in South-Western Ontario and have maintained a database of test results since 2002. We collected demographic information and vital statistics from the Registered Persons Database, and we estimated neighbourhood income levels using Statistics Canada census data [34]. We also collected diagnostic information and physician service claims data from the OHIP database.

Participants

Cohort eligibility and rationale. In order to estimate GFR for all participants, we restricted cohort entry to those with at least one serum creatinine measurement. These measurements were available beginning 1 January 2002. Outcome ascertainment began on this date and continued to 31 March 2008, the last date for which complete data were available. To ensure all cohort members had at least one full year of medication use data, we restricted entry to those aged 66 years and older as of 31 March 2008. Finally, to exclude diet-controlled diabetes, we included only patients with at least one prescription for a diabetes therapy.

Cases and controls. We studied patients separately in groups determined by renal function ('normal' or 'impaired', defined by their most recent eGFR). In each of the two studies, we defined cases as cohort members who presented to an emergency room or hospital with an admission diagnosis of hypoglycaemia. We identified these events by detecting hypoglycaemia diagnosis codes in either the CIHI-DAD or NACRS databases (ICD-9 codes 250.8, 251.0, 251.1, 251.2 or 962.3; ICD-10 codes E10.63, E11.63, E13.63, E14.63, E15, E16.0, E16.1 or E16.2). For patients with multiple hypoglycaemic events during the study period, only the first event was counted. The date of the hypoglycaemic event served as the index date. For each case, we randomly selected up to four cohort patients who at the time of the index date had no evidence of a hypoglycaemic event during the study period. These controls were matched to cases on age at the index date (±1 year) and sex.

Exposure status. For all patients, we searched the ODB database in the 120-day interval immediately preceding the index date to identify prescriptions for diabetes therapies. The ODB formulary provided coverage for the following diabetes therapies: acarbose, gliclazide, glyburide, glimepiride, chlorpropamide, tolbutamide, metformin, pioglitazone, rosiglitazone, nateglinide, repaglinide and multiple formulations of insulin. To simplify interpretation, we excluded patients with prescriptions for more than one type of diabetes therapy in the 120 days prior to the index date. Patients with a prescription for metformin served as the reference group for comparison with each of the other drugs. Patients with prescriptions for different insulin formulations were all deemed to be taking insulin.

Renal function. Using the abbreviated Modification of Diet in Renal Disease (MDRD) formula [35], we used the most recent serum creatinine value prior to the index date to calculate each patient's eGFR. For the primary analysis, patients with an eGFR <60 mL/min/1.73 m^2 were considered to have impaired kidney function while those with an eGFR ≥60 mL/min/1.73 m^2 were considered to have normal renal function. All serum creatinine measurements during the study period were calibrated for use in the MDRD formula.

Potential confounders. Point estimates of risk were adjusted for multiple baseline characteristics, confounding diagnoses and medication exposures (see Supplementary data).

Statistical methods

Baseline characteristics. We used standardized differences to compare baseline characteristics between case and control groups, and groups receiving different diabetes therapies. This metric describes differences between group means relative to the pooled standard deviation and is deemed significant if >10% [36,37].

Primary analysis. We conducted the primary analysis separately for each of the two studies. Using conditional logistic regression, we estimated OR and 95% confidence intervals (95% CI) describing the risk of hypoglycaemia for glyburide and insulin compared to metformin. We forced four variables well associated with hypoglycaemia into the regression models (Charlson score, hospital discharge within 30 days prior to index date, infection within 21 days prior to index date and liver disease). We included other variables based on their performance in bivariate testing. Those having an association with hypoglycaemia with a two-sided P-value ≤ 0.2 were included in the regression model. We used a two-tailed Type I error rate of <0.05 as the threshold for statistical significance. We conducted all analyses with SAS 9.1.3 software (SAS Institute, Carey, NC).

To assess interaction between specific diabetes therapies and renal function, we compared the drug-specific adjusted OR that were determined separately for the impaired and normal kidney function groups using the technique of Altman and Bland [38].

Additional analyses. Altered definition of impaired renal function: To explore the effect of altering the definition of impaired renal function, we repeated the primary analysis using eGFR cutoff values of 45 and 30 mL/min/1.73 m^2.

Table 1. Baseline characteristics for cases and matched controls

	Normal renal function		Impaired renal function	
	Control $n = 802$	Case $n = 204$	Control $n = 1290$	Case $n = 354$
Demographics				
Age at index date				
66–74	326 (40.6)	84 (41.2)	417 (32.3)	112 (31.6)
75–84	371 (46.3)	93 (45.6)	616 (47.8)	174 (49.2)
≥85	105 (13.1)	27 (13.2)	257 (19.9)	68 (19.2)
Female	397 (49.5)	102 (50.0)	660 (51.2)	183 (51.7)
Income quintile				
≤2	368 (45.9)	89 (43.6)	555 (43.0)	167 (47.2)
≥3	432 (53.9)	115 (56.4)	729 (56.5)	187 (52.8)
Comorbidity[a]				
No. of distinct prescriptions in last year	10 (7–14)	13 (10–19)[b]	13 (9–17)	15 (11–21)[b]
Charlson score				
≤1	349 (43.5)	56 (27.5)[b]	452 (35.0)	79 (22.3)[b]
2	103 (12.8)	48 (23.5)[b]	192 (14.9)	53 (15.0)
≥3	157 (19.6)	76 (37.3)[b]	430 (33.3)	188 (53.1)[b]
Missing[c]	193 (24.1)	24 (11.8)[b]	216 (16.7)	34 (9.6)[b]
Hospital discharge within 30 days	21 (2.6)	33 (16.2)[b]	62 (4.8)	43 (12.1)[b]
Infection within 30 days	63 (7.9)	30 (14.7)[b]	113 (8.8)	62 (17.5)[b]
Liver disease	35 (4.4)	16 (7.8)[b]	56 (4.3)	23 (6.5)[b]
Alcoholism	9 (1.1)	6 (2.9)[b]	13 (1.0)	6 (1.7)
Coronary artery disease	253 (31.5)	94 (46.1)[b]	637 (49.4)	211 (59.6)[b]
Congestive heart failure	148 (18.5)	65 (31.9)[b]	478 (37.1)	177 (50.0)[b]
Cerebrovascular disease	163 (20.3)	66 (32.4)[b]	320 (24.8)	101 (28.5)
Number of primary care visits	1 (0–3)	2 (0–3)[b]	1 (0–3)	1 (0–3)
Number of internist visits	1 (0–4)	4 (1–8)[b]	2 (0–7)	6 (2–10)[b]
Previous hypoglycaemic event	10 (1.2)	20 (9.8)[b]	58 (4.5)	38 (10.7)[b]
Kidney function				
Serum creatinine, mg/dL	0.9 (0.7–1.0)	0.9 (0.7–1.0)	1.4 (1.2–1.7)	1.6 (1.3–2.0)[b]
eGFR mL/min/1.73 m^2	76 (68–87)	74 (67–87)	46 (35–53)	40 (28–50)[b]
Most recent eGFR category				
Normal: ≥90 mL/min/1.73 m^2	171 (21.3)	39 (19.1)	–	–
Normal: 60–89 mL/min/1.73 m^2	631 (78.7)	165 (80.9)	–	–
CKD III: 30–59 mL/min/1.73 m^2	–	–	1,081 (83.8)	247 (69.8)[b]
CKD IV: 15–29 mL/min/1.73 m^2	–	–	168 (13.0)	83 (23.4)[b]
CKD V: <15 mL/min/1.73 m^2	–	–	41 (3.2)	24 (6.8)[b]
Hypoglycaemic medications				
β-Blockers	249 (31.0)	69 (33.8)	564 (43.7)	168 (47.5)
ACE inhibitors	433 (54.0)	118 (57.8)	740 (57.4)	209 (59.0)
Hyperglycaemic medications				
Corticosteroids	34 (4.2)	15 (7.4)[b]	72 (5.6)	37 (10.5)[b]
Thiazide diuretics	194 (24.2)	38 (18.6)[b]	346 (26.8)	78 (22.0)[b]
Atypical antipsychotics	39 (4.9)	14 (6.9)	56 (4.3)	23 (6.5)[b]
Diabetes therapy use				
Glyburide	140 (17.5)	53 (26.0)	335 (26.0)	109 (30.8)
Metformin	545 (68.0)	27 (13.2)	551 (42.7)	29 (8.2)
Insulin	117 (14.6)	124 (60.8)	404 (31.3)	216 (61.0)

Note: Data presented as number (percent) or as median (interquartile range). In accordance with Ontario privacy law, patient values <6 are not reported. In accordance with Ontario privacy law, patient values <6 are not reported. Conversion factors for units: serum creatinine in mg/dL to mol/L, ×88.4.
Abbreviations: eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; ACE, angiotensin-converting enzyme.
[a]Comorbidity data were obtained for the 5 years prior to the index date unless otherwise specified.
[b]Indicates a standardized difference between cases and controls >10%. Standardized differences are less sensitive to sample size than tradition hypothesis testing. They express the difference between the means of two populations as a proportion of the pooled standard deviation [36,37].
[c]Charlson scores were based on previous hospitalizations and are only missing where patients did not have a previous hospitalization.

Results

Participants

Over the accrual period, we identified 19,620 patients aged 66 years and older with one or more serum creatinine levels who had at least one prescription for a diabetes therapy. Within this cohort, 364 patients with impaired kidney function experienced a hypoglycaemic event after use of a single drug. We identified 207 such cases among those with normal kidney function. Matching was relatively complete with only 13 cases excluded for lack of a matched control (10 from the impaired kidney function group and three from the normal kidney function group). Although we recorded exposure data on all diabetes therapies in the province-wide drug formulary, only metformin, glyburide and insulin provided enough data for meaningful analysis.

Table 2. Baseline characteristics for users according to diabetes therapy used

	Normal renal function			Impaired renal function		
	Metformin *n* = 572	Glyburide *n* = 193	Insulin *n* = 241	Metformin *n* = 580	Glyburide *n* = 444	Insulin *n* = 620
Demographics						
Age at index date						
66–74	244 (42.7)	57 (29.5)[b]	109 (45.2)	179 (30.9)	111 (25.0)[b]	239 (38.5)[c]
75–84	259 (45.3)	95 (49.2)	110 (45.6)	282 (48.6)	220 (49.5)	288 (46.5)
85+	69 (12.1)	41 (21.2)[b]	22 (9.1)	119 (20.5)	113 (25.5)[b]	93 (15.0)[c]
Female	278 (48.6)	95 (49.2)	126 (52.3)	309 (53.3)	216 (48.6)	318 (51.3)
Income quintile						
≤2	253 (44.2)	102 (52.8)[b]	102 (42.3)	246 (42.4)	203 (45.7)	273 (44.0)
≥3	319 (55.8)	89 (46.1)[b]	139 (57.7)	330 (56.9)	240 (54.1)	346 (55.8)
Comorbidity[a]						
No. of distinct drugs in last year	10 (7–14)	10 (8–14)	13 (9–17)[c]	11 (8–15)	13 (9–17)[b]	16 (12–20)[c]
Charlson score						
≤1	270 (47.2)	69 (35.8)[b]	66 (27.4)[c]	259 (44.7)	127 (28.6)[b]	145 (23.4)[c]
2	61 (10.7)	35 (18.1)[b]	55 (22.8)[c]	83 (14.3)	65 (14.6)	97 (15.6)
≥3	96 (16.8)	47 (24.4)[b]	90 (37.3)[c]	125 (21.6)	172 (38.7)[b]	321 (51.8)[c]
Missing[d]	145 (25.3)	42 (21.8)	30 (12.4)[c]	113 (19.5)	80 (18.0)	57 (9.2)[c]
Hospital discharge within 30 days	17 (3.0)	15 (7.8)[b]	22 (9.1)[c]	25 (4.3)	23 (5.2)	57 (9.2)[c]
Infection within 30 days	45 (7.9)	17 (8.8)	31 (12.9)[c]	51 (8.8)	47 (10.6)	77 (12.4)[c]
Liver disease	26 (4.5)	7 (3.6)	18 (7.5)[c]	25 (4.3)	13 (2.9)	41 (6.6)[c]
Alcoholism	6 (1.0)	<6	7 (2.9)[c]	6 (1.0)	7 (1.6)	6 (1.0)
Coronary artery disease	162 (28.3)	74 (38.3)[b]	111 (46.1)[c]	217 (37.4)	245 (55.2)[b]	386 (62.3)[c]
Congestive heart failure	99 (17.3)	39 (20.2)	75 (31.1)[c]	155 (26.7)	196 (44.1)[b]	304 (49.0)[c]
Cerebrovascular disease	116 (20.3)	49 (25.4)[b]	64 (26.6)[c]	128 (22.1)	109 (24.5)	184 (29.7)[c]
Number of primary care visits	1 (0–3)	1 (0–3)	2 (0–3)[c]	1 (0–3)	1 (0–3)	1 (0–3)
Number of internist visits	1 (0–4)	1 (0–2)[b]	4 (1–8)[c]	1 (0–4)	3 (0–6)[b]	7 (2–12)[c]
Previous hypoglycaemic event	<6	<6	24 (10.0)[c]	11 (1.9)	19 (4.3)[b]	66 (10.6)[c]
Kidney function						
Serum creatinine, mg/dL	0.9 (0.8–1.0)	0.8 (0.7–1.0)	0.8 (0.7–0.9)	1.3 (1.1–1.5)	1.4 (1.2–1.9)[b]	1.6 (1.3–2.0)[c]
eGFR mL/min/1.73 m^2	76 (68–88)	77 (69–87)	75 (66–87)	49 (41–55)	44 (32–53)[b]	39 (29–49)[c]
Most recent eGFR category						
Normal: ≥90 mL/min/1.73 m^2	124 (21.7)	35 (18.1)	51 (21.2)	–	–	–
Normal: 60–89 mL/min/1.73 m^2	448 (78.3)	158 (81.9)	190 (78.8)	–	–	–
CKD III: 30–59 mL/min/1.73 m^2	–	–	–	532 (91.7)	349 (78.6)[b]	447 (72.1)[c]
CKD IV: 15–29 mL/min/1.73 m^2	–	–	–	44 (7.6)	74 (16.7)[b]	133 (21.5)[c]
CKD V: <15 mL/min/1.73 m^2	–	–	–	<6	21 (4.7)[b]	40 (6.5)[c]
Hypoglycaemic medications						
β-Blockers	179 (31.3)	56 (29.0)	83 (34.4)	232 (40.0)	205 (46.2)[b]	295 (47.6)[c]
ACE inhibitors	303 (53.0)	101 (52.3)	147 (61.0)[c]	337 (58.1)	256 (57.7)	356 (57.4)
Hyperglycaemic medications						
Corticosteroids	27 (4.7)	12 (6.2)	10 (4.1)	31 (5.3)	20 (4.5)	58 (9.4)[c]
Thiazide diuretics	140 (24.5)	44 (22.8)	48 (19.9)[c]	190 (32.8)	98 (22.1)[b]	136 (21.9)[c]
Atypical antipsychotics	29 (5.1)	8 (4.1)	16 (6.6)	23 (4.0)	21 (4.7)	35 (5.6)

Note: Data presented as number (percent) or as median (interquartile range). In accordance with Ontario privacy law, patient values <6 are not reported. In accordance with Ontario privacy law, patient values <6 are not reported. Conversion factors for units: serum creatinine in mg/dL to mol/L, ×88.4.
Abbreviations: eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; ACE, angiotensin-converting enzyme.
[a]Comorbidity data were obtained for the 5 years prior to the index date unless otherwise specified.
[b]Indicates a standardized difference between glyburide and metformin users >10%.
[c]Indicates a standardized difference between insulin and metformin users >10%. Standardized differences are less sensitive to sample size than tradition hypothesis testing. They express the difference between the means of two populations as a proportion of the pooled standard deviation [36,37].
[d]Charlson scores were based on previous hospitalizations and are only missing where patients did not have a previous hospitalization.

Patient characteristics according to hypoglycaemic events and diabetes therapy are shown in Tables 1 and 2. Cases and controls within both renal function groups were similar with respect to age and socioeconomic status; however, case patients were more likely than controls to have significant comorbidities and were more likely to have higher stage CKD. Table 2 shows a similar pattern, with patients prescribed glyburide or insulin more likely to have markers of poor health than those receiving metformin.

Primary analysis

Table 3 displays the results of the primary analysis. In patients with normal kidney function, we found the risk of a severe hypoglycaemic event to be 18-fold higher comparing insulin to metformin (adjusted OR 18.7, 95% CI 10.5–33.5) and 9-fold higher comparing glyburide to metformin (adjusted OR 9.0, 95% CI 4.9–16.4). Unexpectedly, we found that the analogous risks among patients with impaired kidney function were lower for both insulin (ad-

Table 3. Association between diabetes therapy and hypoglycaemia

Normal kidney function

	Cases $n = 204$	Controls $n = 802$	Odds ratio (95% CI) Unadjusted	Adjusted[a]
Insulin	124 (60.8)	117 (14.6)	22.5 (13.4–37.8)	18.7 (10.5–33.5)
Glyburide	53 (26.0)	140 (17.5)	8.1 (4.7–13.9)	9.0 (4.9–16.4)
Metformin[b]	27 (13.2)	545 (68.0)	1.0	1.0

Impaired kidney function

	Cases $n = 354$	Controls $n = 1290$	Odds Ratio (95% CI) Unadjusted	Adjusted[a]
Insulin	216 (61.0)	404 (31.3)	10.5 (6.9–16.1)	7.9 (5.0–12.4)
Glyburide	109 (30.8)	335 (26.0)	6.4 (4.1–10.0)	6.0 (3.8–9.5)
Metformin[b]	29 (8.2)	551 (42.7)	1.0	1.0

Abbreviations: CI, confidence interval.
[a]Adjusted for previous hypoglycaemic events, Charlson comorbidity index (1, 2 or ≥3), recent hospitalization, chronic liver disease, alcoholism, coronary artery disease, congestive heart failure, number of distinct medications used in the previous year (≤5, 6–10, 11–15, 16–20, 21–26 or ≥26), number of internist visits in the previous 5 years (≤5, 6–14 or ≥15), concurrent use of corticosteroids, thiazide diuretics or atypical antipsychotics.
[b]Metformin users served as the reference group.

justed OR 7.9, 95% CI 5.0–12.4) and glyburide (adjusted OR 6.0, 95% CI 3.8–9.5).

We found that renal function did not significantly modify glyburide's hypoglycaemic risk (P for interaction 0.15). However, we did find that insulin's hypoglycaemic risk was significantly attenuated in the setting of impaired renal function (P for interaction < 0.001).

Additional analysis: altered definition of impaired renal function

Table 4 displays the risks of hypoglycaemia that associate with glyburide and insulin when the primary analysis was repeated with stricter definitions of impaired kidney function. For both glyburide and insulin users, we found that the risk of hypoglycaemia attenuates as kidney function decreases.

Discussion and Conclusion

The risk of hypoglycaemia among elderly patients with diabetes is significantly greater for those using insulin or glyburide as compared to metformin. We expected to find an augmented risk among glyburide users with impaired renal function, but no such relationship was observed. Instead, for both glyburide users and insulin users, our data showed less risk when the eGFR was below 60 mL/min/1.73 m^2.

It is not surprising that glyburide and insulin conferred higher risks of hypoglycaemia than metformin. These findings are congruent with those of previous studies [24,39–43]. Less expected was the lack of interaction found between impaired renal function and glyburide use. This contradicts the predictions of existing pharmacokinetic data; however, relying on the delayed clearance of glyburide's weakly active metabolites to explain hypoglycaemic events in these patients discounts the nuanced relationship between renal function and serum glucose concentration.

Table 4. Association between diabetes therapy and hypoglycaemia using two different definitions of impaired renal function[a]

	eGFR (mL/min/1.73 m^2)	Odds ratio (95% CI) Unadjusted	Adjusted[a]
Insulin	<45	11.6 (6.0–22.5)	8.9 (4.3–17.8)
	<30	3.4 (1.3–9.1)	3.2 (1.1–9.5)
Glyburide	<45	7.7 (3.8–15.3)	7.5 (3.7–15.3)
	<30	3.8 (1.4–10.5)	4.7 (1.5–14.1)

Note: In all comparisons, metformin users served as the reference groups.
Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate.
[a]Adjusted for previous hypoglycaemic events, Charlson comorbidity index (1, 2 or ≥3), recent hospitalization, chronic liver disease, alcoholism, coronary artery disease, congestive heart failure, number of distinct medications used in the previous year (≤5, 6–10, 11–15, 16–20, 21–26 or ≥26), number of internist visits in the previous 5 years (≤5, 6–14 or ≥15), concurrent use of corticosteroids, thiazide diuretics or atypical antipsychotics.

The impaired kidney plays a complex and dynamic role in serum glucose control. Reductions in drug clearance, gluconeogenesis and insulin metabolism can predispose patients with CKD to hypoglycaemia [12], but a number of mitigating factors must also be considered. Clinically significant reductions in renal insulin metabolism are uncommon until the GFR falls below 20 mL/min/1.73 m^2 [44]. CKD is associated with peripheral insulin resistance [45–47], even at the earliest stages [48], and derangements in parathyroid hormone concentrations may impair pancreatic insulin secretion [49]. Moen and colleagues recently described the cumulative effect of these hypo- and hyperglycaemic factors, showing that CKD is a risk factor for hypoglycaemia even among patients without diabetes [12]. The protective effect of impaired renal function that we observed may be the result of the interplay between these hypo- and hyperglycaemic features of CKD. Alternatively, there may be other immeasurable factors at play. Our study cannot address the effects of these individual mechanisms, nor can we exclude the effects of unknown or unmeasured confounders. However, our findings do suggest that renally cleared drugs such as glyburide play a role in hypoglycaemia among patients with moderate CKD that is less significant than previously thought.

Our study has a number of strengths. This is the first study to examine drug-specific risks for hypoglycaemia in the context of renal function. We assessed renal function directly using serum creatinine concentrations. Our results are most applicable to patients over the age of 65 years, the largest growing segment of the diabetes population [50]. We had adequate power to assess this uncommon but serious adverse drug reaction, and our administrative data were derived from reliable, broadly inclusive datasets.

Our study's most important limitation is the non-random allocation of diabetes therapies. Physicians chose to prescribe drugs for specific reasons. It is possible that patients

who were perceived to be at higher risk for hypoglycaemia received metformin in lieu of glyburide or insulin, or were more closely monitored. Similarly, if physicians were more concerned with the risk of lactic acidosis than hypoglycaemia, this 'confounding by contraindication' may account for the proportionately lower use of metformin we observed among patients with impaired renal function (Table 1).

The ascertainment of outcome, exposure and covariate data was limited by our reliance on health administrative records. By including only cases of hypoglycaemia severe enough to prompt admission or emergency room treatment, we optimized the validity of our outcome definition but undoubtedly missed mild cases and extremely severe cases that resulted in pre-hospital death. In ascertaining drug use, the ODB database is known to be accurate, but filling a prescription is not equivalent to taking a medication nor to taking it properly. Although we took care to adjust our results for important predictors of hypoglycaemia, the administrative records do not include data on confounding variables such as diet, exercise, innate insulin resistance or the individual's targeted and achieved level of glucose control.

A selection bias pertinent to the issue of glycaemic control could also have affected our findings. It is likely that diabetes was the aetiologic factor for many of our patients' impaired renal function; therefore, this group may have had relatively poor glycaemic control which could be protective against hypoglycaemia.

Our definition of impaired renal function was strong in that it did not rely on administrative codes, but we recognize that eGFR is not a static value. It is conceivable that some patients with an eGFR <60 mL/min/1.73 m^2 prior to the index date had only a transient fall in eGFR and that factors such as infection could contribute to both a reduced eGFR and dysglycaemia. However, previous studies in Ontario have shown that most initial single low values of eGFR using outpatient serum creatinine results have proven persistent with subsequent testing [51].

Finally, we had hoped to compare the hypoglycaemic risks of other diabetes therapies but found that only metformin, glyburide and insulin were in common enough use for meaningful analysis. In conclusion, our findings do not justify the use of glyburide in patients with impaired renal function. Rather, our study supports previous research that has found an increased risk of hypoglycaemia among patients with CKD. Our findings support a multi-factorial model of hypoglycaemia in patients with impaired renal function and deemphasize the role played by renally cleared diabetes therapies.

Supplementary data

Supplementary data are available online at http://ndt.oxfordjournals.org.

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Conflict of interest statement. None declared.

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